Asthma, Cardiac Arrhythmias, and Albuterol Aerosol*

N. A. Martelli, M.D.; A. C. Raimondi, M.D., F.C.C.P.; and J. O. Lazzari, M.D.

Twenty asthmatic patients clinically free of heart disease were studied for the possible arrhythmogenic action of albuterol (salbutamol). Two puffs of either albuterol or placebo were inhaled four times per day on two consecutive days and continuous ECG recordings obtained during each 24-hour period. Sixteen patients had atrial extrasystoles, four with albuterol, one with placebo, and 11 with both drugs. The extrasystoles/hour were 6.55 (23.75 SD) with albuterol and 8.37 (33.82) with placebo, a nonsignificant difference. Ventricular extrasystoles were shown in 11 patients, two with albuterol, two with placebo, and seven during both treatments. The extrasystoles/hour were 2.57 (6.36) and 3.10 (7.61) with albuterol and placebo, respectively. This difference was not significant. These findings suggest that therapeutic doses of albuterol aerosol in asthmatic patients without evidence of heart disease and severe hypoxemia should not be considered a cause of cardiac arrhythmias.

Death from asthma is not an exceptional event; in 1978 there were 1,500 deaths in Great Britain. Despite this impressive figure, the etiology remains uncertain. This is especially true regarding sudden death caused by an unexpected ventilatory arrest or perhaps a cardiac arrhythmia.

The increase in asthma mortality registered in England and Wales between 1961 and 1966 was matched by a significant rise in sales of pressurized aerosols, leading to the suspicion that aerosol abuse might be the cause of the excessive deaths. In this regard, the lack of awareness by physicians and patients alike of the possible dangers of aerosol abuse and the preference for aerosols containing isoprenaline (87 percent of the sales), a nonselective β-agonist with a short duration of effect, both might have contributed to aerosol overuse. The present study was designed to establish whether albuterol, a selective β2-agonist, inhaled from a metered aerosol can cause cardiac arrhythmias in asthmatic patients.

Patients and Methods

Twenty-seven ambulatory patients with asthma (18 women, 9 men; mean age 42.2 years, range 24 to 67) were studied. Criteria for inclusion were as follows: (1) asthma controlled by β-adrenergic aerosol bronchodilators with or without concomitant theophylline or its derivatives and steroids (oral or inhaled); (2) patients able to withhold all drugs for 12 hours before control spirometric evaluation. Criteria for exclusion included: (1) either a clinical history suggestive of or proved gastrointestinal ulcer or diabetes; (2) clinical, ECG (standard 12-lead) or radiographic evidence of cardiovascular disease. Informed consent was obtained from all patients. The trial was conducted on three consecutive days.


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On the morning of the first day, after withholding all antiasthmatic drugs for 12 hours, the patients attended the pulmonary laboratory, where FEV1 and FVC were measured on a dry spirometer (Vitalograph) before and 15 minutes after inhalation of 200 μg of albuterol. Arterial blood was obtained from the radial artery and partial tension of oxygen (PaO2) and carbon dioxide (PaCO2) were measured on Radiometer electrodes. Patients were carefully instructed about the use of pressurized aerosols and trained with placebo aerosol until the inhalation procedure was flawless. Anhydrous slow-release theophylline, 200 mg, and prednisone, 10 mg, were then started and instructed to be taken twice daily (9 AM and 6 PM) during the three days of the trial. All other oral medications were stopped, and patients were allowed to continue the use of their aerosols until 8 PM, when they were discontinued for the rest of the trial. From 9 AM of the second day, two consecutive 24-hour Holter ECG recordings were obtained. An aerosol of either albuterol (100 μg/puff) or placebo (albuterol's vehicle) in identical canisters were randomly allocated (permuted block randomization) to be inhaled on that day, two puffs at 10 AM, 2, 6, and 10 PM. The other aerosol was inhaled in the same manner on the next day.

Patients were unaware of the contents of the aerosols. They kept diaries of all of their activities, the time of aerosol inhalation, the time of going to bed at night and on awakening in the morning, and any symptoms during the recording. Aerosol compliance was assessed by weighing the canisters on a Mettler scale. All Holter recordings were analyzed on an Oxford Medilog II analyzer by an independent observer who was unaware of the drug treatment. The 24-hour recordings obtained during albuterol day and placebo day were analyzed separately. The mean hourly heart rates were obtained, and from them the maximum and minimum hourly heart rates. Also the 24-hour mean heart rate was obtained by dividing the total number of beats by the recording time. The total number of atrial and ventricular extrasystoles were counted separately and expressed as extrasystoles/hour.

Seven of the 27 original patients studied were subsequently excluded for the following reasons: faulty Holter recordings (five patients); self-administered albuterol during the evening of placebo day (one patient); inhalation of one instead of two puffs of albuterol detected by canister weighing (one patient). Table I summarizes the clinical data of the remaining 20 patients. Fourteen had been using metered aerosols regularly and five intermittently for the preceding 3.95 years (1 SD 1.76). Eighteen were using albuterol, 11 were also using beclomethasone dipropionate. One patient was taking beclomethasone dipropionate only.
Table 1—Clinical Details of Patients (N = 20)*

<table>
<thead>
<tr>
<th></th>
<th>Mean ± 1 SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>42.6 ± 12.8</td>
<td>24-67</td>
</tr>
<tr>
<td>FEV₁₀ L</td>
<td>2.2 ± 0.8</td>
<td>1.3-4.2</td>
</tr>
<tr>
<td>% Pred</td>
<td>76.6 ± 22.0</td>
<td>33-106</td>
</tr>
<tr>
<td>FVC, L</td>
<td>3.8 ± 1.1</td>
<td>2.2-5.8</td>
</tr>
<tr>
<td>% Pred</td>
<td>113.5 ± 30.7</td>
<td>71-194</td>
</tr>
<tr>
<td>PaO₂ (n = 18), mm Hg</td>
<td>82.3 ± 8.7</td>
<td>65-99</td>
</tr>
<tr>
<td>PaCO₂ (n = 18), mm Hg</td>
<td>37.2 ± 3.8</td>
<td>31-44</td>
</tr>
</tbody>
</table>

*15 F, 5 M.

Statistical Methods

Comparison of heart rates was made by means of the paired t test and the frequency of extrasystoles with the Wilcoxon's signed rank test. Any value greater than 5 percent was considered nonsignificant.

RESULTS

There were no significant differences (mean ± 1 SD) in maximum hourly heart rate, 106.0 (14.6) and 107.7 (16.6); mean heart rate, 83.9 (9.3) and 84.9 (10.2); and minimum hourly rate, 62.9 (6.9) and 64.9 (8.5), during placebo and albuterol days, respectively. Table 2 shows the prevalence of atrial and ventricular premature beats.

Sixteen patients had atrial extrasystoles, four during albuterol day, one during placebo day, and 11 on both days. The number of atrial extrasystoles per hour was 6.55 (23.75) and 8.37 (33.82) with albuterol and placebo, respectively. This difference was not statistically significant. The hourly number of atrial extrasystoles experienced by four patients only while taking albuterol were 0.04, 0.09, 0.13, and 0.13, respectively. Eleven patients had ventricular extrasystoles, two with albuterol only, two with placebo only, and seven during both treatments. The number of ventricular extrasystoles per hour was 2.57 (6.36) and 3.10 (7.61) with albuterol and placebo, respectively, a difference not statistically significant. Sixty-six percent of patients had fewer than one ventricular extrasystole per hour during both treatments. The presence of either atrial or ventricular extrasystoles bore no relationship to the time of inhalation of the aerosols.

Table 2—Atrial and Ventricular Extrasystoles during Albuterol and Placebo Administration

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Atrial Extrasystoles/hr</th>
<th>Ventricular Extrasystoles/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Albuterol/Placebo</td>
<td>Albuterol/Placebo</td>
</tr>
<tr>
<td>1</td>
<td>2.36/0.69</td>
<td>0/0</td>
</tr>
<tr>
<td>2</td>
<td>0.04/0</td>
<td>0/0</td>
</tr>
<tr>
<td>3</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>4</td>
<td>1.22/0.78</td>
<td>0/0.08</td>
</tr>
<tr>
<td>5</td>
<td>0.08/0.30</td>
<td>0.04/0.21</td>
</tr>
<tr>
<td>6</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>7</td>
<td>0.40/0.40</td>
<td>0.31/0.04</td>
</tr>
<tr>
<td>8</td>
<td>0.63/0.52</td>
<td>0/0</td>
</tr>
<tr>
<td>9</td>
<td>16.31/9.52</td>
<td>9.95/16.52</td>
</tr>
<tr>
<td>10</td>
<td>2.04/2.04</td>
<td>0/0</td>
</tr>
<tr>
<td>11</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>12</td>
<td>0.31/0.36</td>
<td>0.27/0</td>
</tr>
<tr>
<td>13</td>
<td>106.30/151.77</td>
<td>0.73/0.63</td>
</tr>
<tr>
<td>14</td>
<td>0.82/0.86</td>
<td>0.08/0.13</td>
</tr>
<tr>
<td>15</td>
<td>0.13/0</td>
<td>0/0</td>
</tr>
<tr>
<td>16</td>
<td>0.13/0</td>
<td>18.95/17.91</td>
</tr>
<tr>
<td>17</td>
<td>0.09/0</td>
<td>0/0.04</td>
</tr>
<tr>
<td>18</td>
<td>0/0.04</td>
<td>0/0</td>
</tr>
<tr>
<td>19</td>
<td>0/0</td>
<td>21/26.40</td>
</tr>
<tr>
<td>20</td>
<td>0.13/0.04</td>
<td>0/0.04</td>
</tr>
<tr>
<td>Mean</td>
<td>6.55/8.37</td>
<td>2.57/3.10</td>
</tr>
<tr>
<td>SD</td>
<td>23.75/33.82</td>
<td>6.36/7.61</td>
</tr>
</tbody>
</table>

P NS NS

DISCUSSION

Eighty percent of the patients had atrial and 55 percent had ventricular extrasystoles. No other kind of arrhythmia was detected during the trial. The extrasystoles did not differ either in type or frequency from those observed in normal individuals studied by the Holter technique during 24-hour periods. Although there were fewer atrial and ventricular extrasystoles during the inhalation of albuterol than during the inhalation of placebo, the difference did not reach statistical significance. Also, in no case was there a relationship between the appearance of the extrasystoles and the inhalation of either aerosol.

Both fluorocarbons and β₂-adrenergic agonists used in aerosol inhalers for treating asthma are capable, at least theoretically, of inducing cardiac arrhythmias. The "epidemic" of sudden deaths among solvent sniffers in the United States raised the suspicion that fluorocarbons might sensitize the heart to the action of catecholamines during hypoxemia. It has been shown that fluorocarbons at blood levels of 20 to 25 μg/ml can sensitize the heart of conscious dogs to adrenaline and induce arrhythmias. However, to attain these blood levels, it would be necessary for a patient to inhale one puff of albuterol aerosol on every breath for 12 to 24 sequential breaths, a highly unlikely situation.

Beta stimulation increases phase 4 depolarization and hence the rate of discharge of the sinus node and subsidiary pacemakers in the atria and in the His-Purkinje system. In this regard, it has been shown that 8 mg of slow-release albuterol can induce the appearance of arrhythmias in asthmatic patients clinically free of heart disease.

We were not able to show any arrhythmogenic action of albuterol, and there are several possible explanations. Albuterol was not overused because the patients adhered strictly to the standard regimen of 0.2 mg inhaled four times daily. It should be stressed that only about 10 percent of a puff reaches the lungs; therefore, our patients inhaled at best an effective dose of 0.02 mg of albuterol four times daily. They also received 400 mg of theophylline and 20 mg of prednisone.
daily to standardize treatment and provide stability.
The lack of evidence of arrhythmias is remarkable
despite the use of theophylline, which might have
favored their appearance. In addition, ECG recordings
for 24 hours are considered adequate to detect
cardiac arrhythmias in most clinical situations.

What, then, is the relative contribution of pres-
surized β2-agonist aerosols to asthma mortality? While
it seems possible, but at present unproved, that the in-
halation of a β2-agonist from a pressurized aerosol
might trigger a fatal arrhythmia in an old patient with
heart disease and severe hypoxemia, it must be re-
membered that a very high proportion of patients dy-
ing of asthma are younger than 45 years old, when
heart disease should be less frequently expected.

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