

Additive Effects of Isoproterenol-phenylephrine Aerosol Following Ipratropium Bromide on Airway Obstruction in Older Patients with Intrinsic Asthma and Chronic Bronchitis

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The additive bronchodilating effect of isoproterenol-phenylephrine aerosol following ipratropium bromide was examined in seven intrinsic asthmatic patients and seven chronic bronchitic patients. FVC, FEV₁ and Z_{RS} were measured before and 30 min. after inhalation of ipratropium, 40 µg. Then inhalation of isoproterenol, 600 µg and phenylephrine, 570 µg was added and the pulmonary functions were measured 30 min. later. The age, baseline values of FVC and FEV₁, and the increases in FEV₁ and 1/Z_{RS} with ipratropium did not differ between the two. Isoproterenol-phenylephrine aerosol following ipratropium produced further increases in FEV₁ and 1/Z_{RS} in asthmatic patients but no additive increases in bronchitic patients. These findings indicate that the role of autonomic nervous system, especially adrenergic system, on *airway* obstruction may be different between asthmatic and bronchitic patients and the method applied in this study may be helpful in differentiating these *airway* disorders.

Key Words: Beta-adrenergic agent, Anticholinergic agent, Intrinsic bronchial asthma, Chronic bronchitis

Current concepts of the control of *airway* caliber in normal humans have been built around the dominance of the parasympathetic system, which is modulated by sympathetic-adrenergic system¹⁾. But it has not been known how the relation between these autonomic nervous systems is altered in humans with airway obstruction.

Airway obstruction in asthmatic and chronic bronchitic patients has been reviewed to be responsive to inhaling anticholinergic agents as well as adrenergic agents. In bronchitic patients, compared with adrenergic agents, anticholinergic agents have been reported to be either as effective or frequently more effective²⁻⁵⁾. In asthmatic patients, adrenergic agents have been said to be

marginally more potent than ipratropium, an anticholinergic drug, in intrinsic asthma and significantly more potent than ipratropium in extrinsic asthma^{6, 7)}. Further, it has been reported that ipratropium was likely to be more effective than adrenergic agents in asthmatic patients older than 40 years of age and less effective in younger patients⁶⁾.

This study was designed to investigate whether the relation between cholinergic and adrenergic systems on airway obstruction in older patients with intrinsic asthma was different from that in age-matched patients with chronic bronchitis.

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MATERIALS AND METHODS

Fourteen inpatients of the Pulmonary Division of the Fukui Cardiac Center were studied (Table 1). Individuals with glaucoma, symptomatic prostatic hypertrophy, bladder neck obstruction, or significant cardiac, renal, hepatic, or metabolic diseases were excluded. In seven of the patients, the principal pulmonary diagnosis was chronic bronchitis⁸. The other seven patients were diagnosed as having intrinsic asthma⁸. All of these asthmatics had bronchial hyperreactivity to inhaled acetylcholine, but no previous history of allergy. They usually developed asthmatic symptoms in association with acute or chronic respiratory infection. At the time of testing, each patient was clinically stable on an established medication regimen. One with asthma and 4 with bronchitis had been cigarette smokers until they were admitted to our division; these patients did not smoke for at least 2 weeks prior to testing. All oral bronchodilators, antihistamines and anti-allergic drugs and coffee and tea were excluded for at least 12 hours prior to testing and all nebulized bronchodilators were excluded for at least 8 hours. None of the patients received steroid therapy for at least one week. The mean age of asthmatic patients was 65.6 years (range, 49 to 78) and that of bronchitic patients was 67.3 years (range, 57 to 78). Informed consent was obtained from all the patients.

Testing started at 2:00 to 3:00 P.M. in the laboratory. Ventilatory function was determined by measuring forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) (PFL M100, SRL Medical Inc., Dayton, Ohio, USA) and respiratory impedance at 3 C/S (Zrs) (MZR-4000, Nihonkoden, Japan). Before the study, patients were trained forced expiration to obtain reliable spiograms. Two measurements of FEV₁, FVC and Zrs were made at one-minute interval and the mean values were calculated. These measurements were performed before, and at 30 minutes and one hour after inhalation of 40 µg of ipratropium bromide (Atrovent, Dai- nippon Pharmaceutical Co. Ltd., Osaka, Japan). Immediately after the second measurement, at 30 minutes, 600 µg of isoproterenol and 570 µg

of phenylephrine were administered from a metered-dose inhaler (Medihaler D, Dainippon Pharmaceutical Co. Ltd., Osaka, Japan). Patients were encouraged to report any side effects.

Statistical analyses were performed using a two-tailed student's t-test for paired data⁹ and the Mann-Whitney U test¹⁰.

RESULTS

Baseline values of FVC and FEV₁ showed no difference between asthmatic and bronchitic patients (Table 1). However, the mean value of Zrs (6.4 ± 0.8 cmH₂O/1/sec, mean \pm SE) in the group with intrinsic asthma was significantly ($p < 0.05$) greater than that (4.5 ± 0.4 cmH₂O/1/sec) in the group with chronic bronchitis.

In patients with asthma, the first inhalation of ipratropium produced significant improvements in FEV₁ ($p < 0.05$, Fig. 1) and Zrs ($p < 0.01$, Fig. 2), and the second inhalation of isoproterenol-phenylephrine produced further, statistically significant, improvements in these measurements ($p < 0.05$ in FEV₁, Fig. 1, $p < 0.05$ in Zrs, Fig. 2).

In patients with chronic bronchitis, the first inhalation of ipratropium produced significant improvements in FEV₁ ($p < 0.01$, Fig. 1) and Zrs ($p < 0.01$, Fig. 2). However, the second inhalation of isoproterenol-phenylephrine did not produce any more improvements in these parameters.

In the groups with asthma and bronchitis, the mean values of FVC increased with the first inhalation of ipratropium and additionally increased

Table 1. Mean Values (\pm S.E.) for Age, Height, Weight and Pulmonary Functions for Asthmatic and Bronchitic Patients.

| | Bronchial asthma (n=7) | Chronic bronchitis (n=7) |
|--------------------------------|------------------------|--------------------------|
| Age | 65.6 \pm 3.6 | 67.3 \pm 2.9 NS |
| Sex | male 3, female 4 | male 6, female 1 |
| Body height (cm) | 152.0 \pm 3.7 | 155.7 \pm 1.8 NS |
| Body weight (kg) | 53.1 \pm 3.4 | 57.0 \pm 3.2 NS |
| FVC, % pred. (%) | 76.6 \pm 6.5 | 83.3 \pm 5.0 NS |
| FEV ₁ , % pred. (%) | 67.5 \pm 5.8 | 73.1 \pm 8.9 NS |
| FEV ₁ % (%) | 58.9 \pm 5.6 | 59.1 \pm 5.9 NS |
| Zrs (cmH ₂ O/1/sec) | 7.0 \pm 0.7 | 4.6 \pm 0.4 * |

* = $p < 0.05$, NS = insignificant difference

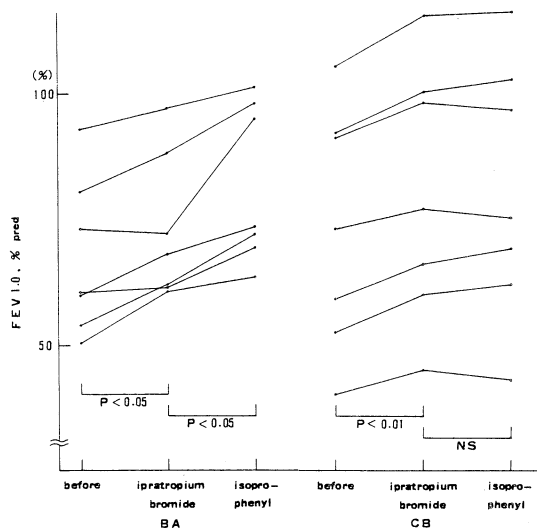


Fig. 1. Values of FEV₁ (% pred.) before and after inhalation of ipratropium bromide followed by isoproterenol-phenylephrine in seven patients with intrinsic asthma (BA) and seven patients with chronic bronchitis (CB). NS = insignificant difference

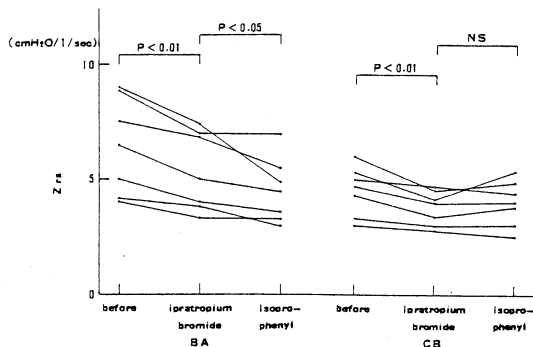


Fig. 2. Values of respiratory impedance at 3 C/S (Zrs) before and after inhalation of ipratropium bromide followed by isoproterenol-phenylephrine in seven patients with intrinsic asthma (BA) and seven patients with chronic bronchitis (CB). NS = insignificant difference

with the second inhalation of isoproterenol-phenylephrine. But, statistically, the increases in FVC were not significant except for that with isoproterenol-phenylephrine in the bronchitic group (Fig. 3).

Fig. 4 summarizes the percent increases in FVC, FEV₁ and 1/Zrs with ipratropium followed by isoproterenol-phenylephrine in seven asthmatic pa-

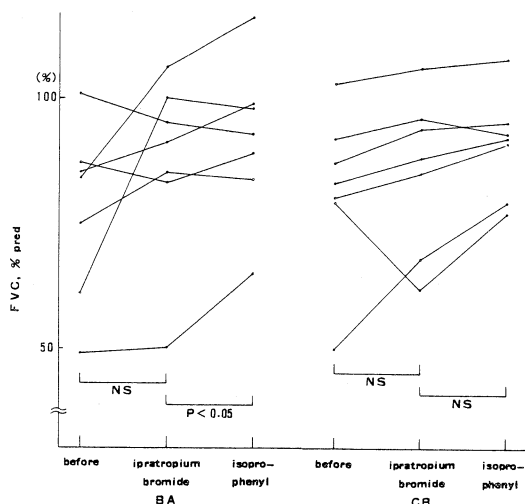


Fig. 3. Values of FVC (% pred.) before and after inhalation of ipratropium bromide followed by isoproterenol-phenylephrine in seven patients with intrinsic asthma (BA) and seven patients with chronic bronchitis (CB). NS = insignificant difference

tients and seven bronchitic patients. Although the improvement in FEV₁ with the first inhalation of ipratropium in both groups approximated, the additive improvement in FEV₁ in the asthmatic group ($13.3 \pm 3.2\%$) with the second inhalation of isoproterenol-phenylephrine was significant ($p < 0.01$) but that in the bronchitic group ($0.4 \pm 1.5\%$) was not significant. In the asthmatic group, the total percent increase in FEV₁ ($22.0 \pm 3.1\%$) after the inhalation of isoproterenol-phenylephrine following ipratropium was significantly ($p < 0.01$) greater than that ($10.7 \pm 2.3\%$) in the bronchitic group. Similar results were obtained for the percent increase in 1/Zrs ($20.8 \pm 3.9\%$) with ipratropium in the asthmatic group was not different from that ($19.0 \pm 4.4\%$) in the bronchitic group. But, in the asthmatic group, the total percent increase in 1/Zrs ($40.9 \pm 7.6\%$) with isoproterenol-phenylephrine following ipratropium was significantly ($p < 0.001$) greater than that ($14.2 \pm 3.0\%$) in the bronchitic group.

No side effects were reported by the group with intrinsic asthma or chronic bronchitis.

DISCUSSION

In this study, isoproterenol-phenylephrine aro-

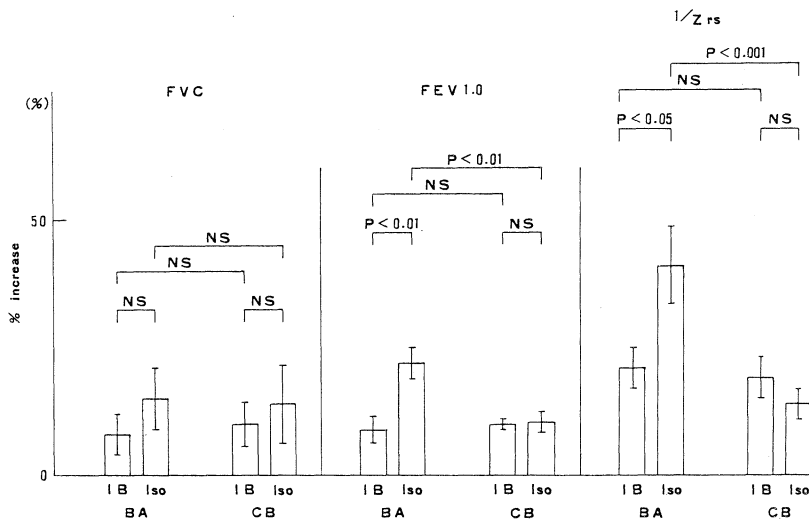


Fig. 4. Mean percent increases in FVC, FEV₁ and 1/Zrs before and after inhalation of ipratropium bromide followed by isoproterenol-phenylephrine in seven patients with intrinsic asthma (BA) and seven patients with chronic bronchitis (CB). The bars indicate standard error (S.E.).

IB = after inhalation of ipratropium bromide

Iso = after inhalation of isoproterenol-phenylephrine following ipratropium bromide

NS = insignificant difference

sol was used as an adrenergic agent because it is available for the treatment of asthma as well as selective β_2 -adrenergic stimulants, such as salbutamol aerosol, and has fewer side effects than isoproterenol alone. Our preliminary study in normal subjects showed that the degrees of increases in FEV₁ and 1/Zrs following isoproterenol-phenylephrine aerosol were not different from those following isoproterenol aerosol, and that rash and palpitation occurred in one of nine and two of nine, respectively, after inhaling isoproterenol alone, while no side effect was observed after isoproterenol-phenylephrine aerosol.

Astin³⁾ showed that reversibility of airway obstruction to bronchodilators was proportional to the degree of initial airway obstruction. Ullah and his associates⁶⁾ showed that ipratropium was more effective in asthmatic patients aged over 40 than in younger patients. In this study, there were no differences in the ages or the baseline spirometric measurements between asthmatic and bronchitic patients. To our knowledge, no previous study has ever been performed on the effects of anticholinergic and adrenergic agents on airway

obstruction in older patients with intrinsic asthma compared to age-matched subjects with chronic bronchitis.

Previous studies^{11, 12)} have shown that bronchodilating effect of ipratropium was not significantly different in asthmatic patients and those with bronchitis and our data showed similar results in older subjects with these conditions.

Lightbody and his associates¹¹⁾ reported that the combination of ipratropium and salbutamol produced much greater increase in FEV₁ than did either alone, but the bronchodilating effect of the combination was not different in asthmatic patients aged 13 to 60 years (mean, 36.5) and bronchitic patients aged 38 to 70 years (mean, 52.0). In contrast, the addition of isoproterenol-phenylephrine aerosol produced further bronchodilation than did ipratropium alone in patients with asthma, but did not produce any changes in patients with bronchitis, in this study. In our preliminary study, the additive bronchodilating effect of isoproterenol-phenylephrine aerosol was not different from that of isoproterenol alone in normal subjects and that of Salbutamol in asth-

matic and bronchitic patients. Therefore, it is unlikely that the discrepancy between our findings and those of Lightbody et al is due to phenylephrine. It would, however, in part, depend on the degree of the reversibility of airways obstruction, because chronic bronchitic patients with reversible airway narrowing were selected as the bronchitic subjects in Lightbody's study¹¹⁾. Hughes and his associated¹³⁾ showed that the increase in FEV₁ with a combination of fenoterol and ipratropium was not different from that with ipratropium alone in pulmonary emphysema.

In conclusion, the relation between cholinergic and adrenergic systems on airway obstruction in older patients with intrinsic asthma may be different from that in subjects of similar ages with chronic bronchitis because additive bronchodilating effect of inhaling adrenergic agents on airways pretreated with anticholinergic drugs was observed in asthmatic patients, but not in bronchitic patients. The method applied in this study might be useful as a screening test by which asthma could be differentiated from chronic bronchitis or pulmonary emphysema.

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