Effect of Bronchodilation on the Deposition and Clearance of Radioaerosol in Bronchial Asthma in Remission

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Radioaerosol inhalation lung cine-scintigraphy and lung function tests were performed on ten patients with bronchial asthma in remission before and after inhalation of salbutamol following intravenously administered aminophylline. Radioaerosol inhalation lung cine-scintigraphy was very useful in revealing the changes not only in the deposition patterns of inhaled aerosol in the lungs but also in the dynamic transport of mucus on the airways. The bronchodilating effect of the combined treatment was significant; the inhaled aerosol deposited more homogeneously and less centrally in the lungs, the "penetration index" and the alveolar deposition ratio (ALDR) increased from 31 ± 3 to 49 ± 7%, and from 29 ± 2% to 39 ± 1%, respectively, while the airway deposition ratio (ADR) decreased from 72 ± 2 to 61 ± 1% immediately after the treatment. Lung function data including FVC, FEV 1.0, FEV 1.0%, MMF, V50 and Vp significantly improved after the treatment. There was, however, little visual or quantitative improvement in mucociliary clearance after the treatment.

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It is not unreasonable to expect that beta-2 agonists improve the mucociliary clearance mechanism in the lungs, because they are known to show favorable effects on ciliary beats and mucus secretion in vitro (*1–7*). Radioaerosol inhalation lung cine-scintigraphy is useful in dynamically demonstrating the deposition pattern of inhaled radioaerosol in the lungs and how the deposited radioactivity is cleared from the lungs with time; in other words, the mucociliary clearance mechanisms in the lungs (*8–10*).

Previously we tried to demonstrate the "favorable" effect of orally administered salbutamol on the mucociliary clearance mechanisms; however, an accelerated mucociliary clearance could not be substantiated (*8*). A minimum but a significant bronchodilation followed after 7 days' treatment with oral salbutamol, but the treatment did not induce any recognizable changes either in the deposition patterns of inhaled aerosol or in mucociliary clearance before and after the treatment. The patients studied at that time were those with a variety of diseases not necessarily complicated with reversible obstructive airways disease (*8*).

The purpose of the present study was to investigate whether improvement in mucociliary clearance mechanisms would actually occur or not in patients with bronchial asthma in remission who are known to have reversible airway obstruction when bronchodilation was attained by inhaling beta 2-agonist salbutamol following intravenous administration of aminophylline.

MATERIALS AND METHODS

Ten uncomplicated asthmatic patients in remission were selected for the study. There were seven males and three females and their mean age was 60 yr old ranging from 38 to 83. The duration of the illness or the time interval from the first diagnosis of bronchial asthma ranged from 4 to 10 yr with the average of 7 yr. Seven were in normal activity and three were just about to be discharged from hospitalization. They were symptom-free and had not had paroxysmal dyspneic attacks for at least 4 to 6 wk prior to the present studies. All of them were taking minimum maintenance medications consisting of oral bronchodilators, mucolytic agents,

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sodium cromoglycate, and/or xanthine derivatives. All maintenance therapeutic regimens were suspended on the day of the study or in other words, for about 16 hours after the evening dose for the previous day. They made no subjective complaints attributable to bronchoconstriction after the temporary withdrawal of the maintenance therapy. No patients were current smokers. They did not have any known allergy to chemicals, foods, pollen, dusts or mites.

Physical examinations, chest x-rays, lung function tests, arterial blood gas analysis and radioaerosol inhalation lung cine-scintigraphy were done and all the data obtained served as controls for the subsequent studies. A week later the same studies were repeated immediately after patients received the following treatment; infusion of 250 mg aminophylline in 200 ml normal saline followed by inhalation of 0.2–0.3 ml of 0.5% salbutamol solution through a motor-driven jet nebulizer. Each treatment took ~30 min.

Radioaerosol inhalation lung cine-scintigraphy was done as described previously (*9–11*). In brief, ultrasonically generated technetium-99m albumin aerosol (mass median diameter 3.73 μm, with geometric s.d. 1.73) (*12*) was inhaled through the mouth with the nose clipped in resting tidal breathing with the patient in the sitting position. After ~3 mCi of radioactivity deposited inside the thorax after inhaling for 1 to 3 min depending on the initial radioactivity in the nebulizer which ranged from 40 to 100 mCi, the patient lay supine comfortably under a gamma-camera connected to a computer. Radioactivity was continuously measured in sequential frame mode from anteriorly for 60 min. Three hundred and sixty 10-sec frames were collected and stored in the computer.

First, aerosol deposition patterns in the lungs were inspected. Second, dynamic features of the mucociliary transport inside the thorax was observed on radioaerosol inhalation lung cine-scintigraphy which was edited from the 360 frames for a cine-mode presentation reported previously (*9–11*). Third, for quantitative analysis, the 360 frames were sequentially divided into six parts, each representing a sequential 10-min process consisting of 60 original frames. These sequential 60 frames were lumped together to make one frame. Thus six new frames were made out of 360 frames in all. Radioactivity in the first new frame covering the initial 10 min after radioaerosol inhalation was the basis for the subsequent calculations and comparisons. Overall lung retention ratio (LRR) for the right and left lungs, or the ratio of radioactivity remaining in the lungs in each of the six new frames relative to the total radioactivity in the first new frame was calculated as previously described (*10,11*). The alveolar deposition ratio (ALDR) or the LRR at 24 hr was calculated from the following formula; $ALDR = -48.08 + 0.47 \times FEV\ 1.0\% + 0.59 \times LRR60$ (*13*), where FEV 1.0% is forced expiratory volume in 1 sec (FEV 1.0) divided by forced vital capacity (FVC), and LRR 60 (overall lung retention ratio (LRR) at 60 min) both expressed in %. As reported previously, derivation of this formula has made it unnecessary to repeat measurement of remaining radioactivity in the lungs at 24 hr (*13*).

Radioactivity in the right lung was quantitatively analyzed from the six newly made-up frames. In defining the border of the right lung, we set a cutoff level of 3% of the initial maximal counts per matrix in the right lung of the first made-up frame after the treatment (*10*), because inhaled aerosol deposited more homogeneously after the treatment than before the treatment, showing a larger lung size. The same lung border was applied to all the newly made-up frames of the right lung before and after the treatment so that we could compare the distribution and disappearance of radioactivity in the same-sized right lung. Lung retention ratio (LRR), airway deposition ratio (ADR), or (LRR minus ALDR), which means the amount of radioactivity remaining throughout the ciliated airways relative to the total radioactivity initially deposited in the lungs in each made-up frame, and airway clearance efficiency (ACE) which indicates what percentage of radioactivity deposited on the ciliated airways has already been cleared by time t, for the right lung were calculated by using the ALDR as described above (*10,11*).

To separate the right lung into two regions which contained more and less of the major airways, respectively, the right lung was divided into two as shown in Figure 1; the ones whose matrixes contained 25% or more of the maximal counts per matrix in the right lung in the first made-up frame before the treatment and the remainder, respectively. The latter was called

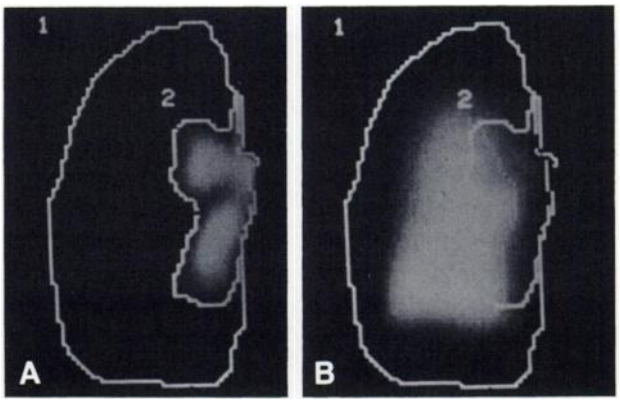

FIGURE 1
The right lung was divided into two regions as indicated. Region 1: The lung border indicating 3% of the maximal counts per matrix in the right lung before the treatment. Region 2: The line indicating 25% of the maximal counts per matrix in the right lung before the treatment. A: Before the treatment (Case 1). B: After the treatment (Case 1). The area surrounded by lines 1 and 2 was called the peripheral lung region.

the peripheral lung region. The "penetration index" was calculated by dividing radioactivity in the peripheral lung region by total radioactivity in the right lung in the first made-up frame.

Paired t-test was used for statistical analysis. P less than 0.05 was considered statistically significant.

RESULTS

Physical Examination and Chest X-Rays

Physical examination revealed neither wheezing nor significant tachycardia nor finger tremor before and after the treatment. Chest x-rays remained unchanged in the week's interval.

Lung Function and Blood Gas Data

Forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV 1.0), FEV 1.0 divided by FVC in % (FEV 1.0%), maximum midexpiratory flow rate (MMF), expiratory flow rate at 50% of FVC (V50) and peak flow rate (Vp) significantly increased after the treatment ($p < 0.05$) but lung volume compartments and diffusing capacity did not change after the treatment. Arterial blood gases did not show any significant changes, either, but arterial oxygen tension (PO2) tended to show some decreases after the treatment.

Deposition Patterns of Inhaled Aerosol

In nine of the ten patients inhaled aerosol deposited more centrally before the treatment, but aerosol deposition became more homogeneous throughout the lungs after the treatment.

Mucociliary Transport Patterns

Visual inspection of radioaerosol inhalation lung cine-scintigraphy indicated that there were only minor differences in mucociliary transport patterns (*9–11*) before and after the treatment.

Alveolar Deposition Ratio (ALDR)

The ALDR significantly increased from 29 ± 2 (17–35), mean ± s.e. (range) % before the treatment to 39 ± 1 (32–44) % after the treatment ($p < 0.01$) as shown in Figure 2. The 95% confidence interval in the normal subjects (n = 24) was from 36.5 through 47.5% (*14*).

Quantitative Analysis for the Right Lung

"*Penetration index*". The average "penetration index" was 31 ± 3% before the treatment and increased to 49 ± 7% after the treatment as shown in Figure 3. The difference was statistically significant ($p < 0.01$). Roughly speaking, aerosol deposition patterns of those whose "penetration indexes" were <30% or so were visually recognized as central deposition patterns although there were exceptions to this generalization.

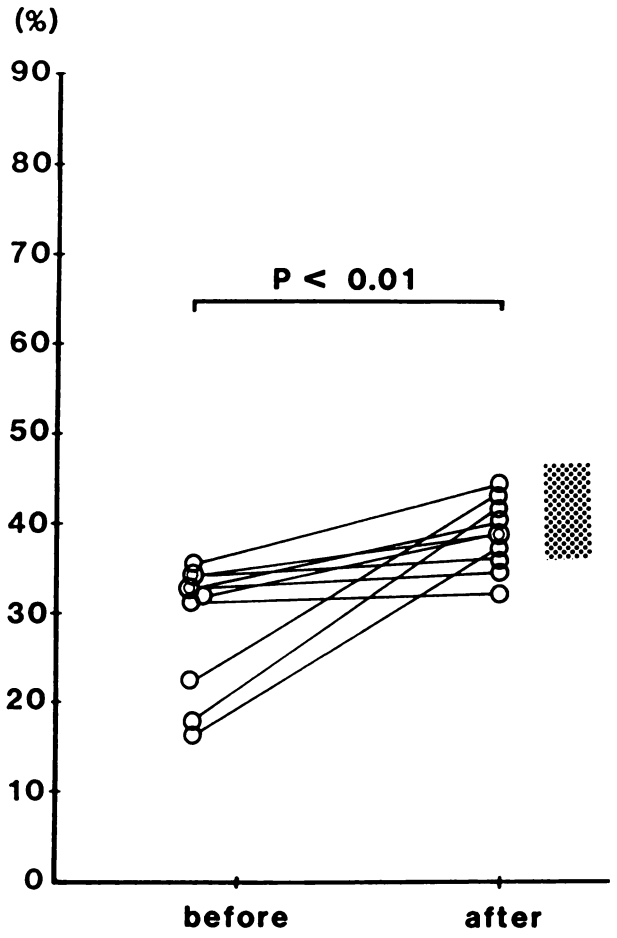

FIGURE 2
Changes in alveolar deposition ratio (ALDR) before and after the treatment. The shaded band indicates the 95% confidence interval in the normal subjects (n = 24) (*14*).

Lung retention ratio (LRR). Although the LRR's after the treatment appeared to show greater values both in the right whole lung and in the peripheral lung region than the respective ones before the treatment, there was no significant statistical difference by paired t-test before and after the treatment (Fig. 4A).

Airway Deposition Ratio

The airway deposition ratio (ADR) immediately after aerosol inhalation showed significantly larger values before than after the treatment ($p < 0.0001$) both in the right whole lung and in the peripheral lung region but there was no significant difference thereafter (Fig. 4B).

Airway Clearance Efficiency

The airway clearance efficiencies (ACEs) were smaller after the treatment both in the whole right lung and in the peripheral lung region than before the treatment (Fig. 4C), but the difference was not statistically significant.

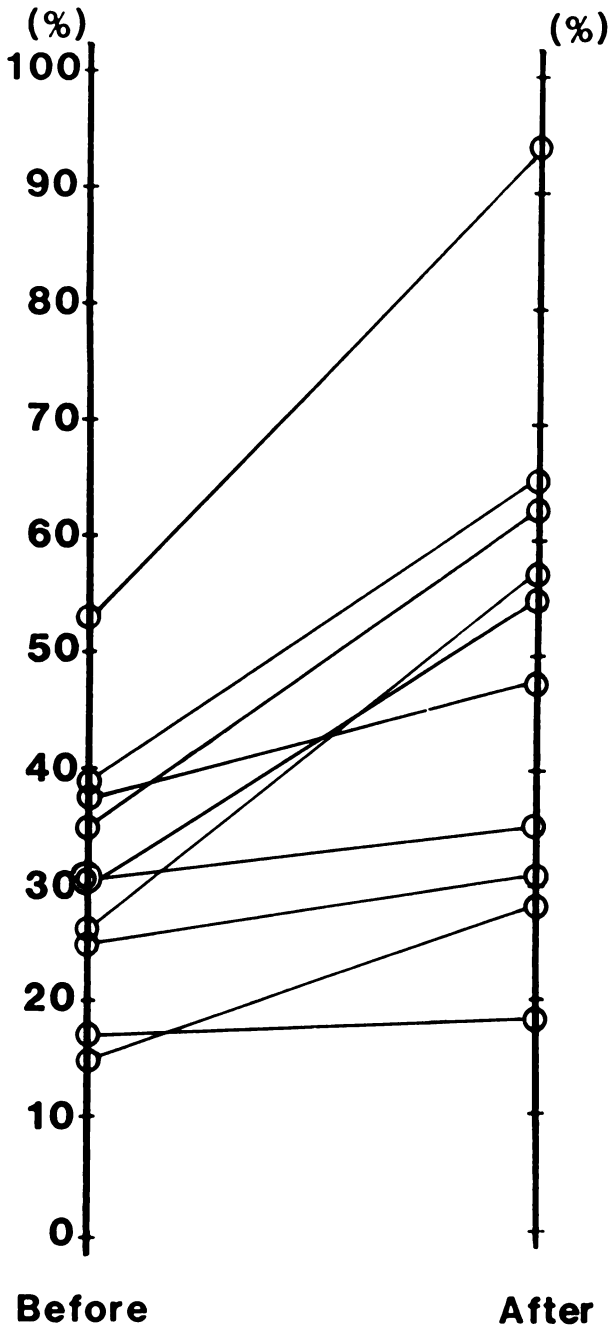

FIGURE 3
Changes in "penetration index" before and after the treatment.

DISCUSSION

In response to a marked bronchodilation after the treatment, radioaerosol deposition patterns became more homogeneous throughout the lungs with less radioaerosol depositing on the central major airways (Fig. 1). Quantitatively speaking, the alveolar deposition ratio (ALDR) and the "penetration index" increased after the treatment (Figs. 2 and 3). The airway deposition ratio (ADR) consequently decreased immediately after the treatment. Mucociliary transport patterns were, however, definitely abnormal before and after the treatment, and very little influence of the treatment on mucociliary transport patterns and clearance itself was recognizable.

In a sense, it was surprising that the symptom-free patients with bronchial asthma in remission could respond to the treatment with bronchodilators. Although we clinicians are liable to take it for granted that if asthmatic patients are symptom-free, they must have nearly normal lung function, actually they don't (*15*). Despite bronchodilation, however, there was but little change in mucociliary clearance function. The ten patients with bronchial asthma in remission were selected for this study because it is reported that in patients with stable asthma or asthma in remission, the mucociliary transport is slower (*16–18*) and that beta 2-agonists stimulate ciliary beats and mucus secretion in vitro (*1–7*). Etiology of bronchial asthma in our patients was not allergy, but the so-called intrinsic or idiopathic in nature and chronic in duration.

Sympathomimetic agents are believed to act in part at least by enhancing adenylcyclase levels and increasing the quantity of cyclic AMP (adenosine monophosphate) in mediator-secreting cells with resultant inhibition of mediator-secretion. Methyl xanthines inhibit the effects of phosphodiesterase and maintain cyclic AMP at a high level by a mechanism which is quite different from that of salbutamol (*19*). Thus we can expect synergistic effects on bronchodilation and possibly on mucociliary clearance mechanisms, although there is a report that aminophylline adds to the toxicity but not the efficacy of an inhaled beta-stimulator in the treatment of acute exacerbations of asthma (*20*). Favorable effects of methyl-xanthines on mucociliary clearance are also reported (*21–23*).

Not only in the baseline studies but also after treatment our asthmatic patients didn't necessarily show either significantly slower or accelerated mucociliary clearance. We do not know exactly why our patients with bronchial asthma in remission showed as a group nearly as fast a mucociliary clearance as in normal subjects. Mossberg and others also report a similar result in asthmatics as a group (*24*). Our asthmatic patients had been placed on minimum maintenance therapeutic regimens, but these medications were suspended on the day of the study or for at least 16 hr or so since the last dose before the patients were studied. We did not discontinue the medications longer than this because we thought a longer withdrawal of medications unwise in fear of inducing dyspneic attacks in symptomless patients. Thus we cannot rule out the possibility of some residual pharmacological effects were present when studies were made.

There is a belief that aerosol clearance is faster in the central than peripheral airways (*17,25*). If this is so, there could be a slowing in clearance solely on the basis

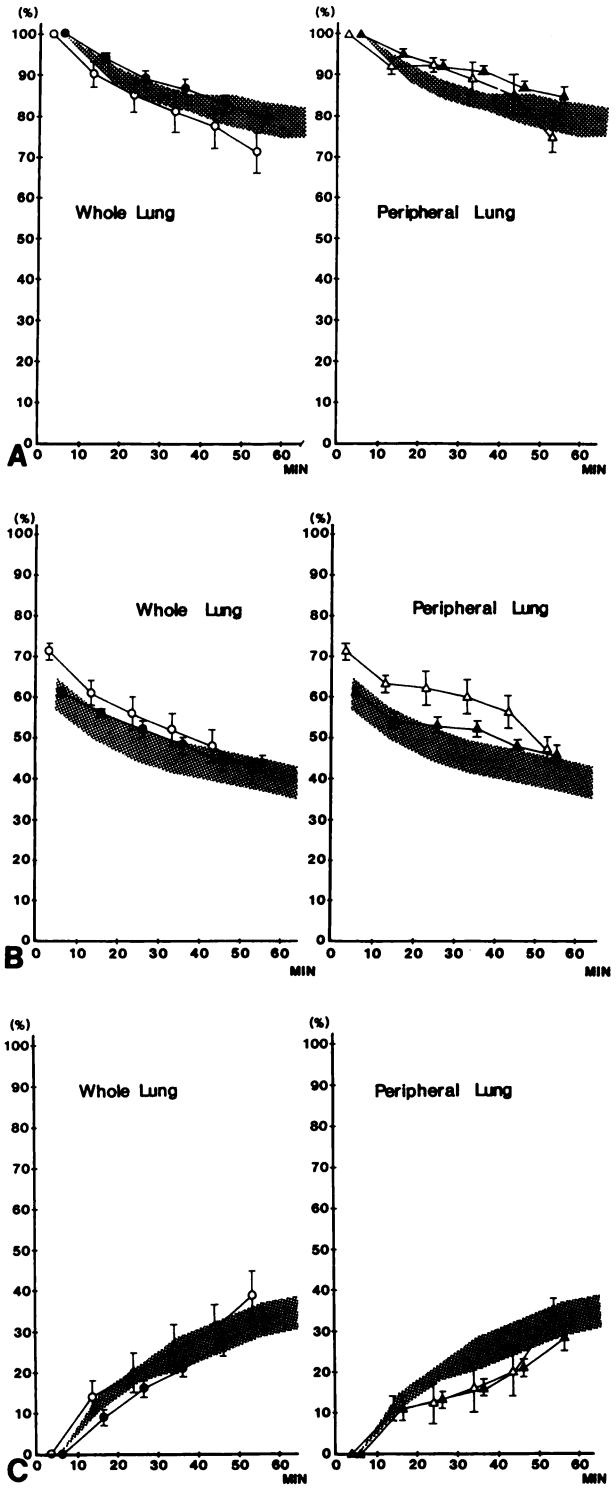

FIGURE 4
A: Lung retention ratios; B: Airway deposition ratios; and C: Airway clearance efficiencies in the right whole lungs and peripheral lung regions before (○, △) and after (●, ▲) the treatment, respectively. Airway deposition ratio in the first 10 min was significantly larger before the treatment than after the treatment ($p < 0.01$).

of altered deposition after the treatment, because bronchodilation led to more peripheral aerosol deposition. To clarify this point, we tried to evaluate the mucociliary clearance mechanisms not only in the right whole lung but also in the right peripheral lung region excluding the central major airways.

As could be seen, there was no statistically significant difference in the airway clearance efficiency (ACE) in the peripheral lung region even after the treatment. Of the regional LRR, ADR and ACE in the peripheral lung, the only significant difference was in the airway deposition ratio (ADR) immediately after the treatment, confirming that more aerosol deposited in the peripheral airways after the treatment. Thus we couldn't tell from this kind of analysis whether the mucociliary clearance was stimulated or not in the peripheral airways after the treatment.

The ADR at each time means that the fraction of inhaled aerosol that initially deposited on the ciliated airway mucosa that still remains there at that specific time (*10,11*). Thus if we subtract ADR 60 from ADR 10 and divide the difference by 60 min, we can roughly estimate the mean disappearance rate of radioactivity from the ciliated airways in terms of %/min. Here we name this index the mean airway disappearance rate (MADR). If the MADR increases after the treatment, we might be able to judge that the treatment has facilitated the mucociliary clearance function. Our MADR is quite similar to the average lung clearance rates in normal subjects reported by Foster and others (*17*). Previously we compared the changes in ACE to evaluate the pharmacological effect on the mucociliary clearance function (*8,26*).

No significant effect of the treatment with inhaled salbutamol following aminophylline infusion on the mucociliary clearance mechanisms has been substantiated in our patients with bronchial asthma in remission by any method of analysis. The present results have also confirmed what we found with oral salbutamol (*8*).

Another way of thinking would be that the impaired mucociliary clearance mechanisms if correctable had already been corrected in those asthmatic patients who had been on maintenance regimens to the extent that any further improvement was not feasible. In our previous study, little change was noted in mucociliary clearance function after oral salbutamol was given for 7 days as compared with before the treatment (*8*).

As far as bronchodilating effect is concerned, salbutamol inhalation following intravenous aminophylline has resulted in a more marked bronchodilation than the administration of oral salbutamol for 7 days (*8*). We could tell the marked bronchodilating effect of the treatment both visually by radioaerosol inhalation lung cine-scintigraphy and quantitatively by lung function tests, but further facilitation of the mucociliary clearance by the treatment was not documented. The patient might get subjectively and objectively favorable benefits from bronchodilator therapy because the airways have

actually been dilated and less coughs occur due to lesser stimuli to the peripheral cough receptors secondary to bronchodilation (*27*). Contribution of mucociliary clearance to the patient's sense of well being would be minimal if any.

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