Mucociliary Clearance and Transport in Bronchiectasis: Global and Regional Assessment

Toyoharu Isawa, Takeo Teshima, Tomio Hirano, Yoshiki Anazawa, Makoto Miki, Kiyoshi Konno, and Masakichi Motomiya

Department of Medicine, The Research Institute for Chest Diseases and Cancer, Tohoku University, Seiryoumachi, Sendai, Japan

Global and regional mucociliary clearance and transport in the lungs was studied in 20 patients with bronchiectasis by radioaerosol inhalation lung cine-scintigraphy and the quantitative analysis following inhalation of ultrasonically-generated ^{99m}Tc-tagged human serum albumin aerosol (mass median diameter; 1.93 μm with geometric s.d. of 1.52). In bronchiectatic lung regions, deposition of inhaled aerosol was diminished or inhomogeneous. Transport of inhaled radioactivity from the bronchiectatic regions was deranged in 95% of the patients (19/20). The following abnormal mucous transport patterns were regionally observed; stasis in 12 of the 20 patients (12/20), regurgitation or reversed transport in 14/20, straying in 8/20, spiral or zigzag transport in 1/20, and/or various combinations of these four abnormal transport patterns. When coughs occurred, regurgitation and stray became more marked in the bronchiectatic regions. These regional abnormalities in mucociliary transport seem to be responsible for the development of infections and hemoptysis in the bronchiectatic regions.

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It is known that in bronchiectatic regions, both ventilation and perfusion are diminished (*1,2,3*). Restrictive or obstructive disturbance or both is documented as lung functional derangement in patients with bronchiectasis (*4,5,6*). Much is not known yet, however, as to how mucociliary clearance or mucous transport mechanisms actually functions in the bronchiectatic regions of the lungs (*7,8,9*). No one has reported findings in mucous transport or mucociliary clearance in the bronchiectatic regions from the standpoint of visual observation of the function. We have studied mucociliary clearance function in 20 patients with bronchiectasis by radioaerosol inhalation lung cine-scintigraphy, which enables the actual visualization of the dynamic mucociliary transport in the lungs as it is (*10,11,12*). A quantitative analysis of time-activity curves was made to obtain the lung retention ratio, airway deposition ratio, airway retention ratio, airway clearance efficiency, and alveolar deposition ratio (*11,12*), and the time-activity curves were qualitatively evaluated.

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For reprints contact: Toyoharu Isawa, MD, Department of Medicine, The Research Institute for Chest Diseases and Cancer, Tohoku University, 4-1 Seiryoumachi, Aoba-ku, Sendai 980, Japan.

MATERIALS AND METHODS

Twenty hospitalized patients with bronchiectasis, 18 to 81 yr of age, were studied. Their mean age was 48 yr. Nine were male and 11 were female. Their chief complaints on admission were hemoptysis in 10, increased sputum production in 9, and chest pain in 1. Bronchopulmonary neoplasms, tuberculosis, aspergillosis, cardiovascular diseases, pulmonary vascular diseases such as thromboembolism, hemosiderosis or blood-clotting disorders were ruled out. The diagnosis of bronchiectasis was established by bronchography either during the current hospitalization or prior to admission. Three had bronchiectasis only in the right, eight only in the left, and nine in both the right and the left lungs. Nineteen of the 20 patients showed involvement of the lower lobe bronchi. Seventeen showed bronchiectasis dominantly of cylindrical type, two, varicose, and one, saccular (*13*). Past history indicated pneumonia or bronchial asthma in infancy in 11, sinusitis in 2, and pulmonary tuberculosis, lung abscess or increased coughs of adult onset without known causes in 7. Sputum culture on admission indicated hemophilus influenzae in 12, pseudomonas aeruginosa in 4, alpha streptococci in 3 and peptococcus in 1. Vital capacity (VC) averaged 74% of the predicted, and in 10 of the 20 patients it was less than 70% (*14*). Forced expiratory volume in 1 sec divided by forced vital capacity (FEV1%) averaged 68%, and in 10 of the 20 patients it was <70%. Lung function test, chest x-rays, blood-gas analysis, and perfusion lung imaging were done in all patients within 3 days of aerosol inhalation studies. All 20 patients were on mucolytic agents such as bromhexine and 10 on beta-stimulators. Four were ex-smokers who had not smoked in over 5 yr, and there was only one current smoker of 60 pack-years.

When the patients were afebrile and stable with less coughs and sputum production, they were studied with radioaerosol inhalation lung imaging as follows; ultrasonically generated technetium-99m- (^{99m}Tc)-albumin aerosol (mass median diameter 1.93 micron with geometric s.d. of 1.52 (*15*)) was inhaled with the patient in the sitting position with normal tidal breathing through the mouth with the nose clipped and immediately after completion of aerosol inhalation the mouth was rinsed and radioactivity of the thorax was measured from the anterior by a gamma camera with the patient in the supine position. Approximately 3 mCi (111 MBq) deposited in the thorax immediately following inhalation. Radioactivity was continuously recorded to a computer in a frame mode of 10 sec each for over 90 to 120 min. Following the measurement of radioactivity in the supine position as described above, anterior, posterior and right and left lateral views of radioaerosol inhalation lung images were taken with the patient in the sitting position.

Radioaerosol inhalation lung cine-scintigraphy was compiled from the 540 or 720 10-sec frames and the distribution of inhaled radioaerosol and the dynamic mucociliary transport patterns were visually inspected in the bronchiectatic regions as well as globally in the whole lungs including the trachea (*10,11,12*). Mucous transport patterns such as stasis or, in other words, temporary but frequent stopping and starting of radioactivity in the airways in the course of mucous transport, regurgitation or reversal of mucous transport, straying or migration of radioactivity from one region to another of the same lung or from one lung to the opposite lung, and spiral or zigzag motions or winding paths of radioactive clusters instead of the usual axial course were recorded in the bronchiectatic regions (*12*).

Regions of interest (ROIs) including the entire right lung, the entire left lung, the bronchiectatic and the nonbronchiectatic lung regions were demarcated over the right and left lungs with a light pen and respective regional time-activity curves were obtained from those ROIs. Bronchiectatic regions were demarcated manually with the aid of bronchography, aerosol inhalation, and perfusion lung imaging. The latter usually showed a decreased or absent perfusion in the bronchiectatic regions. After physical half-life correction of the time-activity curves, net time-activity curves from the ciliated airways were obtained by subtracting from the corrected original regional time-activity curves the corresponding regional radioactivity, equivalent to the one that deposited in the distal nonciliated airways, including the alveolar space that we called "alveolar deposition ratio" (*11,12,16*). Calculation of quantitative parameters such as lung retention ratio, airway deposition ratio, airway retention ratio, airway clearance efficiency, alveolar deposition ratio (*11,12*), and disappearance rate of radioactivity from the ciliated airways (*17*) were made for the entire right and the entire left lungs separately or the right and left lungs in combination. Data were compared with corresponding values obtained from 36 normal subjects (*17*). Comparison of the corrected time-activity curves between bronchiectatic and nonbronchiectatic ROIs was made.

Unpaired and paired Student t-tests were used for statistical analysis.

RESULTS

Cine-Scintigraphic Observation

The deposition of inhaled aerosol in the bronchiectatic lung regions were decreased or nearly absent in 18 and inhomogeneous in 2 of the 20 patients. All but one showed abnormal mucous transport patterns in the bronchiectatic regions such as stasis (12/20), regurgitation (14/20), stray (8/20), and spiral or zigzag motion (1/20), while in the normal lung regions no particular abnormality in mucous transport was visually noted.

Time-Activity Curves

Although time-activity curves from any normal lung regions smoothly declined with time as shown in Figure 1, those from the bronchiectatic lung regions showed irregularly rising or declining curves (Fig. 2A). Figure 2B–C indicated actual sequential aerosol inhalation lung images of a patient with right lower lobe bronchiectasis, who showed time-activity curves as shown in

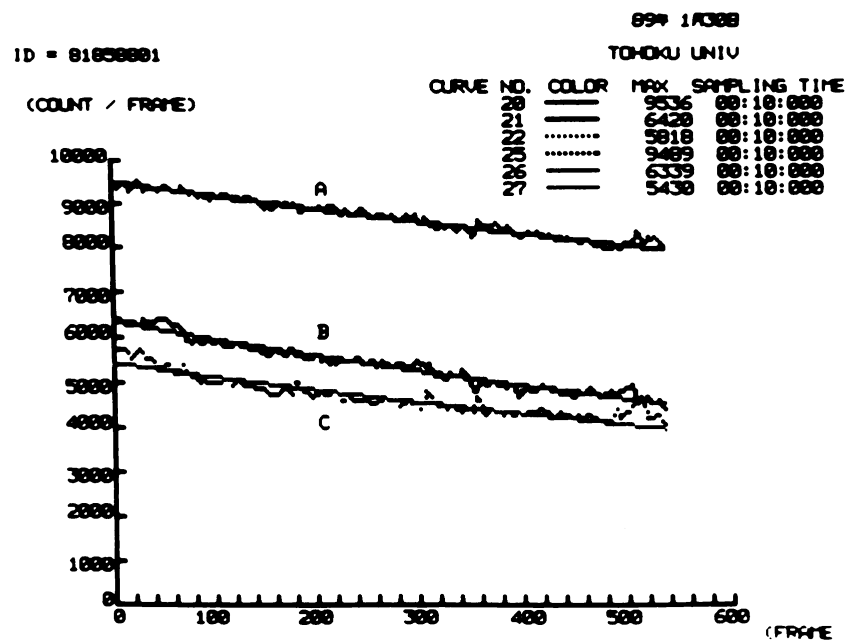

FIGURE 1
Curves A, B, and C indicate time-activity curves from the entire right lung, the left lung, and the lower half of the right lung, respectively, of a 26-yr-old normal nonsmoker (No. 81858801). Abscissa: frame number (each 10 sec), ordinate: counts per frame. Each superimposed straight line indicates a corresponding exponential function fitted to each time activity curve. In normal lung, time-activity curves from any lung regions show more or less similar steadily declining tendency.

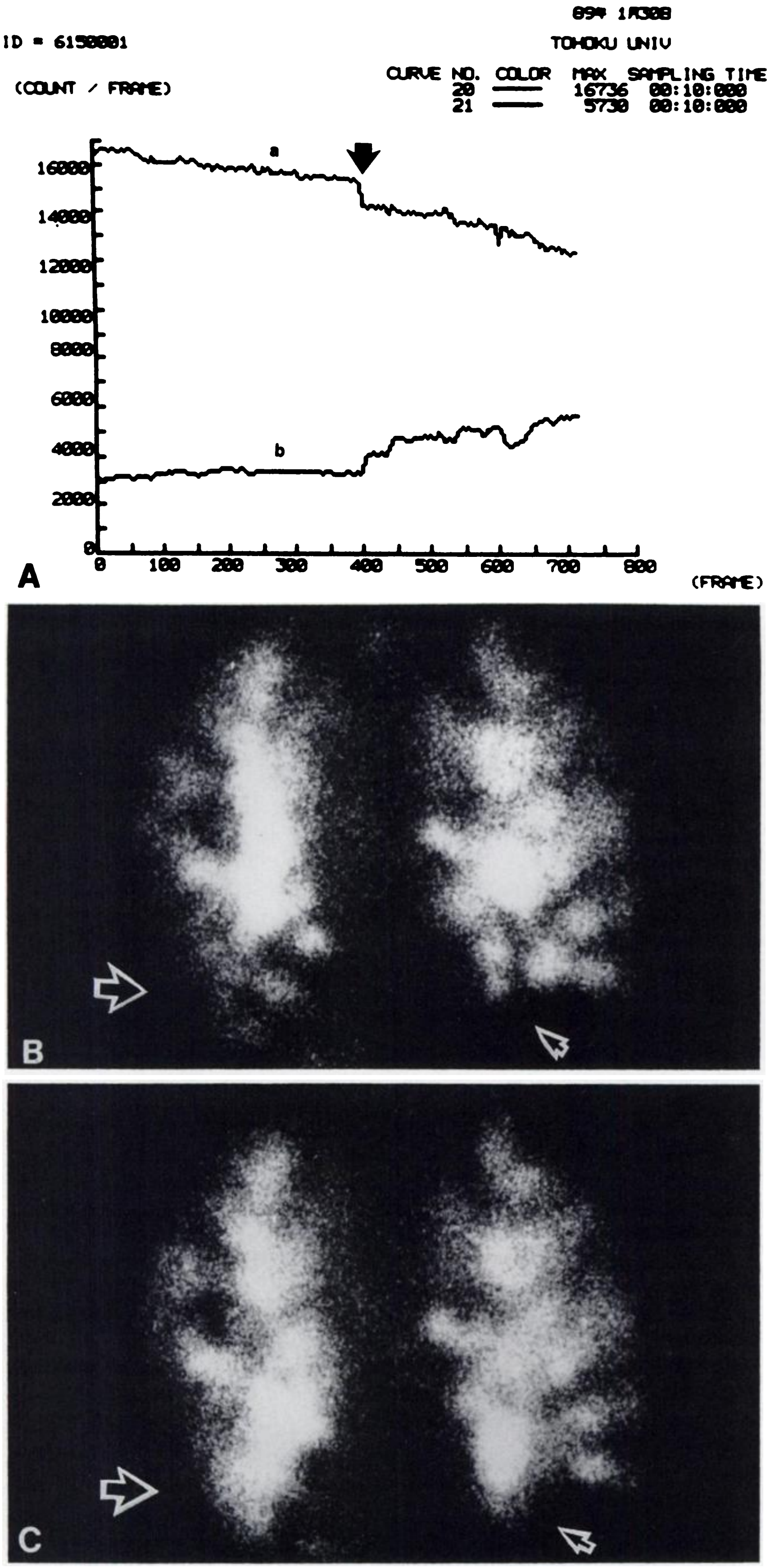

FIGURE 2

(A) The upper (a) and lower (b) curves indicate time-activity curves from the ciliated airways in the upper two-thirds and the lower one-third of the right lung, respectively, of an 81-yr-old male patient (No. 6150001), a current smoker with chronic obstructive airways disease and bronchiectasis of the right lower-lobe bronchi. He developed recurrent pneumonias in the right lower lobe probably due to straying of mucus there with cough from the airways in the upper lung regions and in addition to generalized impaired mucociliary clearance. Both curves initially show nearly horizontal lines and were then interrupted by a sudden decrease and an increase in radioactivity, respectively, indicating a cough (arrow). Following the cough, the upper curve (A) shows irregular but generally declining tendency, while the lower curve (b), a rising tendency. The former indicates a slow mucous transport characterized by stasis and regurgitation, while the latter indicates straying of mucus into the bronchiectatic right base. This patient happened to be studied 10 times over a 4-yr period and always showed a similar pattern. (B) Static aerosol inhalation lung image (anterior) of the same patient before cough between approximate frame numbers 300 and 330. Note that only little radioactivity is present in the right lower lung field (big arrow). Radioactivity in the left base is also diminished (small arrow). (C) Static aerosol inhalation lung image (anterior) after cough between approximate frame numbers 450 and 480. Note that radioactivity in the right base increased after cough, indicating that mucus strayed from the upper airways to the lower bronchiectatic lung region (big arrow). A more or less similar phenomenon was seen in the left base where mild bronchiectasis was also present (small arrow).

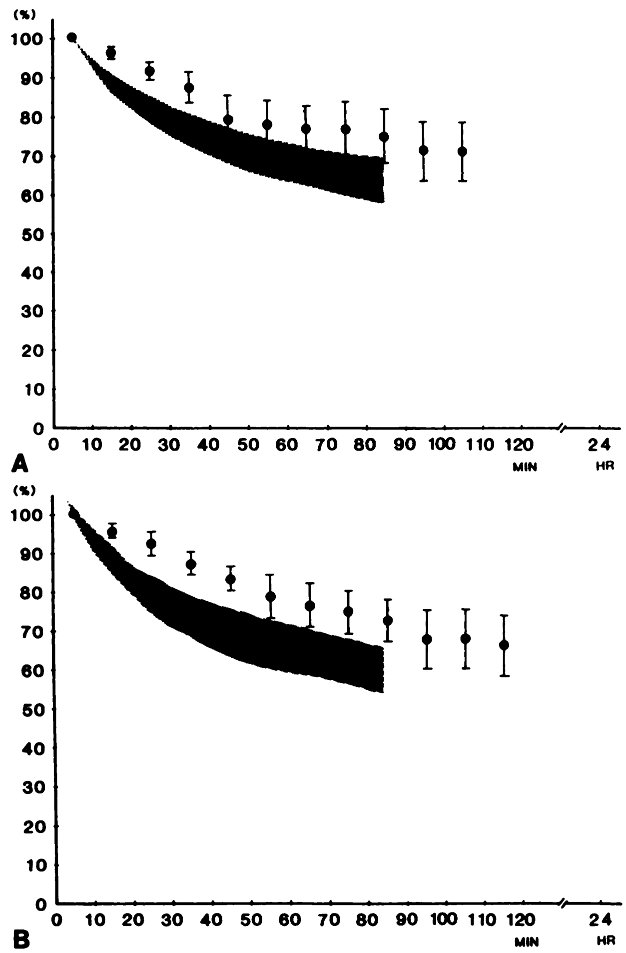

FIGURE 3
(A) Airway retention ratios in the right and left lungs combined in the nine subjects who had bronchiectasis in both lungs. When multiple studies were done in the same subject, the data obtained at the first study was used. Airway retention ratios in the nine patients with bronchiectasis in the right and left lungs were significantly higher than the 95% confidence interval of airway retention ratios in the right and left lungs of 28 normal subjects (17). (B) Airway retention ratios in the left lungs in the eight patients whose bronchiectasis was located only in the left lung. Airway retention ratios in the left lung in the eight patients were significantly higher than the 95% confidence interval of airway retention ratios in the left lungs of 28 normal subjects (17).

Figure 2A (#6150001). Time-activity curves did tell whether mucous transport was normal or not, but they themselves did not specify what kind of abnormal mucous transport patterns were responsible for their irregular shapes.

Quantitative Parameters

The alveolar deposition ratio was significantly smaller in the patients with bronchiectasis (33.7% ± 2.3%; mean ± s.e.e.) as compared with normals (39.2% ± 1.8%) by unpaired Student t-test ($p < 0.05$) (*17*). In patients whose bronchiectasis was present only in the left lung and/or in patients who had bronchiectasis both in the right and left lungs, there was no significant difference in lung retention ratios as compared with normals, but airway retention ratios and airway deposition ratios showed significantly higher values than the 95% confidence intervals of the normals ($p < 0.05$ each) (Fig. 3A–B). Airway clearance efficiency was significantly smaller than normals. The average disappearance rate of radioactivity from the ciliated airways in the bronchiectatic patients was below normal only in the first 30 min following inhalation of aerosol and there was no significant difference thereafter as compared with the 95% confidence interval of the normals.

DISCUSSION

The term bronchiectasis describes bronchial or bronchiolar distortion and scarring leading to abnormal dilatation, peribronchial alveolar tissue damage, obliteration of the distal bronchi or bronchioles and obstructive endoarteritis (*18,19,20*). These anatomical findings may explain regionally abnormal ventilation (*1*) and perfusion (*2,3*) in bronchiectasis. In addition to these anatomical changes, a possible hypoventilation in the bronchiectatic regions may contribute to the decrease in regional perfusion due to hypoxic vasoconstriction (*21,22*). The deposition of inhaled radioaerosol was actually greatly diminished in the regions of bronchiectasis (*7,8,9*), indicating regional hypoventilation (*1*). Bronchiectasis can be either "wet" or "dry" according to the presence or absence of concomitant infection (*18,23*), and various ultrastructural anomalies of cilia have been found and thought to be of pathogenic significance (*23,24,25*). A relatively inefficient cough in ridding bronchiectatic segments of their secretions has been observed by a combined cinefluorographic-manometric study, because the central airway collapse occurs while the bronchiectatic segments remain dilated (*27*). Disturbance in mucociliary clearance is naturally anticipated under these circumstances but little is described regarding what is actually taking place in the bronchiectatic regions in terms of mucous transport.

The most striking abnormality in the bronchiectatic regions was the behavior of radioactivity or in other word mucous transport as observed by radioaerosol inhalation lung cine-scintigraphy. This display modality was developed to see the actual mucociliary transport inside the thorax in vivo (*10,11,12*). By the cine-scintigraphic technique, we have found that there are basically four abnormal transport patterns on the large airways in obstructive airways disease; namely, stasis, regurgitation, stray, and spiral or zigzag motion, whereas in normal nonsmoking subjects mucous transport was always cephalad or axial in direction and nearly constant in velocity (*11,12*). These abnormalities were seen less frequently in interstitial lung diseases (*28*) or in pulmonary vascular diseases (*29*). These visual regional abnormalities on cine-scintigraphy were more or less substantiated by the shapes of the time-activity curves from the ciliated airways in the corresponding lung regions as shown in Figure 2B–C. In the present analysis, normal lung regions showed steadily declining time activity curves (Fig. 1), but those from the bronchiectatic regions showed irregular or abruptly rising or declining curves or nearly horizontal curves interrupted by a declining tendency. These abnormal time-activity curves were confirmed by cine-scintigraphic observation to correspond to regurgitation, straying, stasis, or zigzag motion of the mucous transport (*12*). By looking at only the shapes of time-activity curves, however, no differentiation was possible between the four abnormal transport patterns recognizable by aerosol inhalation lung cine-scintigraphy.

It has been found that coughs are not only inefficient in getting rid of secretions as suggested by Fraser and associates (*27*), but that they are also liable to induce regurgitation and/or straying of mucus into the bronchiectatic regions as shown in Figure 2A–C. All the patients studied were on mucolytic agents and half of the patients were given bronchodilators. Although a mucolytic agent was found to facilitate mucociliary clearance (*30*), beta-stimulators do not seem to do so (*31,32,33*). If pathogen containing mucus reaches the bronchiectatic regions as in cases of straying, regurgitation and stasis, or if mucus produced in the bronchiectatic regions cannot be transported as efficiently as from the normal regions, there would be an ample time for pathogens to multiply in the bronchiectatic lung regions to induce regional inflammatory changes there. Acutely inflamed mucosa on the basis of well developed bronchial circulation (*34*) may tend to bleed. Presence of bronchial arterial hypervascularity and bronchopulmonary anastomosis may even accelerate hemoptysis (*35*).

Whether such abnormal transport patterns have primarily helped develop the bronchiectasis or whether they are the results of bronchiectasis itself remains an unsolved question. The present study confirms the well known fact that bronchiectatic patients are easily infected, and their bleeding (*19*) seems to be explained by abnormalities in mucociliary clearance and/or mucous transport in the bronchiectatic regions. Bronchial hygiene, a trial to keep the bronchiectatic regions "dry" and an unhesitating use of antimicrobial agents at the first sign of infection and on a long-term basis (*36*) would be the best policy in taking care of patients with bronchiectasis.

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