

## Mucociliary Clearance in Health and Disease

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### Airway Mucus and Cilia

Mucociliary clearance is the first line of defense in the respiratory system. The mucus overlying the epithelial surface of the respiratory tract is propelled upward toward the larynx by coordinated beating of the cilia of the airway epithelium. The cilia line the epithelium of the respiratory mucosa from the nasal passages to the terminal bronchioles. In and distal to the terminal bronchiole the cilia are either poorly developed or absent<sup>1)</sup>.

Bronchial surface (the ciliary surface) is covered with mucus layer. Actually the cilia are immersed in the periciliary fluid above which there is a mucus layer. By a coordinated ciliary motion at the rate of about 1,000/min the mucus layer is normally transported toward the oropharynx. Mucociliary clearance or transport is orchestrated by interaction between the mucus layer and ciliary beats<sup>2,3)</sup>.

### Principles of Mucociliary Imaging

For the study of mucociliary clearance mechanisms, bronchoscopic or radiographic methods have

been used but they are mostly invasive requiring anesthesia of the airways and insertion of a bronchoscope<sup>4-7)</sup>.

In order to study mucociliary clearance by external measurement, radioactive materials have been placed on the mucosal surface of the airways and sequential imaging has been made<sup>8-10)</sup>. Documenting the transport of the radioactive substance placed on the mucus layer provides an objective measure of mucociliary clearance.

Acute toxicity of cigarette smoke to mucociliary clearance has been easily evaluated in dogs by this methods as described later. A large field view gamma camera is used for imaging.

Radioactivity is introduced onto the mucosal surface either as a radioactive droplet or as a marker tagging an inert carrier or as inhaled radioaerosols. The former is more or less invasive because it requires anesthesia of the airways and bronchoscopic procedures, whereas the latter, radioaerosol inhalation is noninvasive and readily applicable in clinical practice.

In addition to the lung imaging immediately following radioaerosol inhalation, sequential or follow-up lung images are taken at 30 min, 1, 2, 3 hr to evaluate how mucociliary transport is taking place in the lung, especially in the large airways like the trachea. A qualitative assessment of mucociliary clearance is possible with the delayed imaging method.

An inevitable disadvantage of this delayed imaging however, is the break of continuity from image

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to image. There is no guarantee that a "hot spot" seen on one image is the same one seen on a previous or a subsequent image. Thus the conclusions based on movement of such "hot spots" could end up in error. In this sense the delayed imaging method is not adequate means to study mucociliary clearance mechanisms in vivo in humans. Transport direction or velocity can be determined by this method only when an adequate hot spot is discretely recognized.

In order to avoid the above drawback, radioactivity of the entire thorax including the trachea is continuously measured from immediately following radioaerosol inhalation for 90 to 120 min in sequential 10 sec frame mode in  $64 \times 64$  matrix. Each sequential 10 sec data is recorded and stored in a computer. The raw data is either compiled for cinematographic display that we call "Radioaerosol inhalation lung cinescintigraphy" or utilized for quantitative analysis<sup>11-13</sup>.

"Radioaerosol inhalation lung cine-scintigraphy" is displayed in cine mode on a CRT screen at the rate of 18 framed per sec and the cinematographic display is recorded by a movie-camera or on video-tape. This cinematographic display has enabled visualization of actual mucous transport in the airways in vivo<sup>11</sup>.

## Mechanisms of Aerosol Deposition

Inhaled aerosol deposits on the airways by impaction, sedimentation and diffusion. When turbulence occurs in the airways at the sites of stenosis or narrowing caused by mucous deposition, cancerous protrusion of the airway mucosa, excessive narrowing of the airways in obstructive airways disease, etc., excessive deposition of inhaled aerosol or "hot spots" appear regionally corresponding to the stenotic lesion<sup>14</sup>.

## Agents Used for Studying Mucociliary Clearance

### 1. Radioactive Droplet

Any agent,  $^{99m}\text{TcO}_4$ -(technetium pertechnetate),  $^{99m}\text{Tc}$ -HSA (human serum albumin),  $^{99m}\text{Tc}$ -millimicrosphere,  $^{99m}\text{Tc}$ -albumin microsphere,  $^{99m}\text{Tc}$ -MAA (macroaggregated albumin) that stays on the airway mucous layer following placement through bronchoscopy can be used<sup>15</sup>. A droplet size in the order of 0.025-0.05 ml of  $^{99m}\text{Tc}$ -MAA placed through a tube inserted into the bronchoscope is practically convenient.

Anesthesia of the airway mucosa as well as the oropharynx is required for placing a radioactive droplet on the tracheal or bronchial mucosa. This is tedious and cumbersome and gives so much discomfort to patients that the actual clinical application of this method is limited.

### 2. Radioaerosol

Radioaerosol-generated by either a jet nebulizer, an ultrasonic nebulizer, a spinning - disc atomizer under special circumstances, or other inhalers - is inhaled through a mouth piece with the nose clipped. An agent that is not absorbed or dispersed through the airway mucosa is ideal. Either  $^{99m}\text{Tc}$ -sulfur colloid,  $^{99m}\text{Tc}$ -phytate or  $^{99m}\text{Tc}$ -HSA (human serum albumin) can be used for the study of mucociliary clearance mechanisms. We have usually used  $^{99m}\text{Tc}$ -HSA aerosol generated with a jet nebulizer or an ultrasonic nebulizer.

Aerosols with geometric standard deviation (GSD or  $\sigma$  g) of 1.1 or less are termed monodisperse aerosols, while those with GSD of greater than 1.1 are called polydisperse aerosols.

The size of inhaled radioaerosol, hygroscopy and breathing pattern determine the sites of deposition in the lung<sup>14,16</sup>. The size of various aerosols

is shown in Table 1. We use normal tidal breathing for inhaling radioaerosol.

For studying mucociliary clearance the aerosol size (activity median aerodynamic diameter, AMAD) of less than 5-6 micrometer ( $\mu\text{m}$ ) but greater than 1  $\mu\text{m}$  would be most suitable as shown by Morrow and Yu<sup>17</sup>. The author personally uses <sup>99m</sup>Tc-HSA aerosol of AMAD of 1.93 micron with GSD of 1.52 inhaled by the normal tidal breathing for studying mucociliary clearance in the lungs.

## Experimental Studies in the Dogs

When a single radioactive bolus is placed on the carina or the main bronchus of a normal dog through a vinyl tube under bronchoscopic guidance, the radioactive bolus is transported upward toward the vocal cord at a nearly constant steady velocity.

The transport can be well appreciated by sequential or follow-up imaging. The transport velocity is calculated by dividing the migrating distance of the radioactive bolus by time required for the transport. The transport velocity of normal dogs is about 11-12 mm/min<sup>10</sup>.

When dogs are forced to smoke cigarettes, the transport velocity tends to be slowed down as the number of cigarettes smoked increases. This indicates that the toxicity of the cigarette smoke acutely hinders mucociliary clearance in the normal dogs<sup>10</sup>. Cauterization of the airway mucosa by applying silver nitrate in the normal dog can also damage mucociliary clearance<sup>15</sup>. It takes about 2 weeks for the recovery of the normal mucociliary clearance from either cigarette smoke or cauterization<sup>10,15</sup>. Filtered cigarette does not prevent the mucociliary clearance function from being damaged as the number of cigarettes smoke exceeds a certain level, say 5 cigarettes on running in the normal dog<sup>10</sup>.

## Human Studies

### 1. Delayed Imaging

Because anesthesia of the oropharynx and the upper airways is absolutely necessary for bronchoscopic insertion, the placement of a radioactive droplet on the large airways under bronchoscopic guidance itself is not practical in most clinical situations. Instead inhalation of radioaerosol that is not absorbable from the mucosal surface becomes a method of choice in the daily clinical practice.

When delayed imaging is repeated following radioaerosol inhalation in patients with bronchogenic carcinoma, some show a hot spot in later images either unchanged or larger than that seen on the image produced immediately after inhalation. In others, a hot spot observed on the immediate image disappears on delayed images. The former indicates that the airway mucosa at the site of the hot spot is invaded by cancer cells, while in

**Table 1.** Mass Median Diameter and Geometric Standard Deviation Under Standard Conditions (Temperature: 37°C, Relative Humidity: 100%, and Test Agent <sup>99m</sup>Tc-albumin) Measured by Cascade Impactor (Andersen sampler)

Nebulizer	AMAD ( $\mu\text{m}$ )	$\sigma$ g
Jet nebulizers		
OEM-1 (USA)	1.96	1.65
OEM-2 (USA)	1.19	1.86
Ultravent (USA)	1.04	1.71
Penicilin nebulizer glass (Japan)	1.76	1.70
BARC with reservoir (India)	0.84	1.73
BARC without reservoir	1.57	1.80
Ultrasonic nebulizers		
Mistogen EN142 (USA)	1.93	1.52
Omuron-NE-Ull (Japan)	1.62	1.50
Devibiss (USA)	1.78	1.60

the latter, it is not invaded and the mucociliary clearance remains intact.

While studying mucociliary clearance function by repeated delayed imaging following radioaerosol inhalation, we found the case which was puzzling with regard to interpretation of the behavior of mucous glob. Immediately after aerosol inhalation there was no radioactivity in the left main bronchus. At one hour, delayed imaging revealed a radioactive glob on the left main bronchus that disappeared 2 hours following inhalation. If mucus is always transported in cephalad direction toward the vocal cord, the presence of radioactivity on the left main bronchus is a mystery difficult to interpret. This finding suggests that there must be some inherent defect in this methodology for studying mucociliary clearance. Continuous measurement of radioactivity following radioaerosol inhalation instead of repeated delayed imaging is necessary to know exactly what happens to the inhaled aerosols in terms of mucociliary clearance.

## 2. Radioaerosol Inhalation Lung Cine-Scintigraphy

Following inhalation of ultrasonically generated  $^{99m}\text{Tc}$ -HSA (human serum albumin) aerosol in tidal breathing through a mouth piece with the nose clipped, a subject is placed either under or above a gamma camera in the supine position and radioactivity was measured over the entire thorax including the trachea for 120 min in sequential 10 sec frame mode with  $64 \times 64$  matrices. The data was recorded and stored in a computer. The data was displayed in cine-mode on a cathode ray tube (CRT) screen at the rate of 18 framed per sec and the cinematographic display was recorded in a movie camera. By cinematographic display, dynamic mucous transport patterns in the large airways like the trachea or the main bronchus can be observed and evaluated. This provides the first

opportunity to observe the actual dynamic mucous transport in vivo in the human lungs<sup>11-13</sup>.

## Quantitative Evaluation

### 1. Extrapulmonary Airways

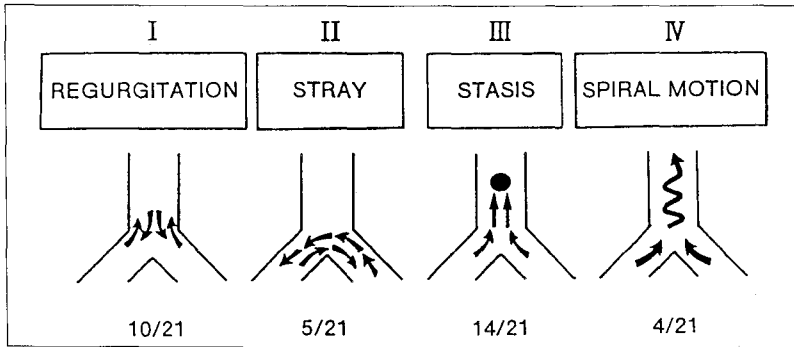
Under an experimental situation as described above (5. Experimental studies in the dogs), transport velocity of a radioactive droplet can be assessed by measuring peak radioactivity of the droplet at two different measuring points and time required for transport between the two spots. Then the distance transported divided by the time required for the transport is equivalent to velocity of the mucociliary clearance. This is only true when the transport is straight and upward in direction and constant in transport velocity.

Under clinical situation, however, the insertion of bronchoscopy itself requires anesthesia, and placing a radioactive droplet on the sensitive trachea gives great discomfort to patients and is thus not practical and nor feasible. Furthermore transport patterns are not always straight and upward in direction. That is why radioaerosol inhalation lung cine-scintigraphy has been developed. Various patterns of mucous transport were observed and appreciated by radioaerosol inhalation lung cine-scintigraphy<sup>11-13</sup> as shown in Fig. 1.

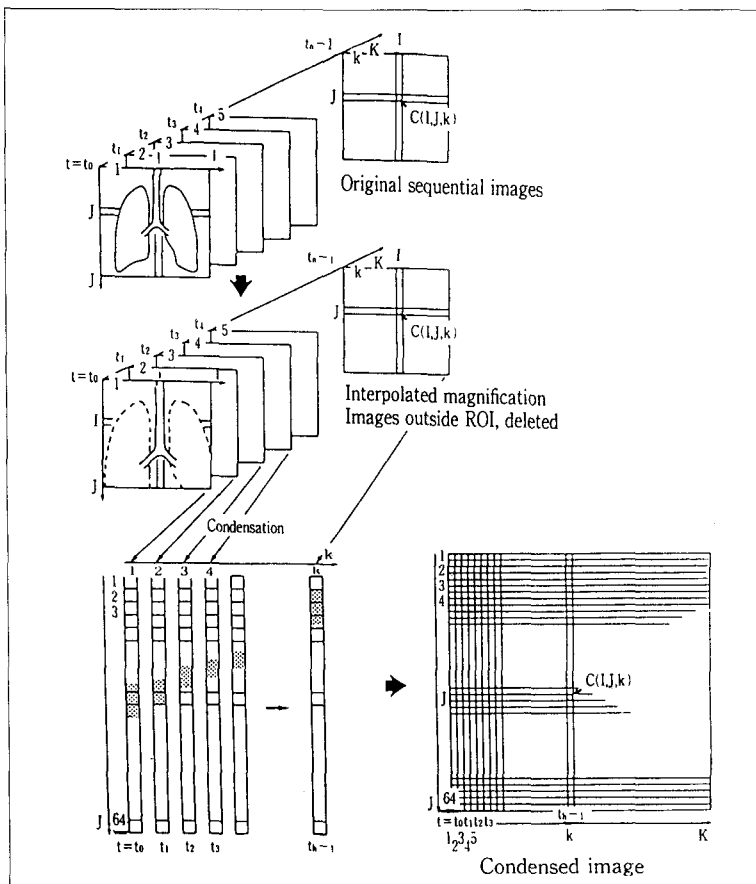
Quantitative analysis was made by the following methods<sup>18</sup>;

#### 1) Condensed Image Mode

The tracheal portion of each frame data is selected and arranged sequentially on a computer as shown in Fig. 2 and displayed on the CRT with its x-axis as time and the Y axis as the distance. When mucous transport is cephalad and straight in direction and constant in velocity, the transport path becomes a diagonal line. When mucous transport is greatly disturbed and the velocity becomes



**Fig. 1.** Four abnormal mucus transport patterns on the trachea. Although steady transport cephalad in direction is seen in normal nonsmokers, the above 4 abnormal mucus transport patterns are observed in combination in pathologic states. In straying only shuttling transport between the opposite bronchi is shown here, straying transport from one region to a different portion inside the same lung is also seen. The numbers below indicate frequency observed in 21 patients with COPD.



**Fig. 2.** Diagram of condensed image mode. Only the tracheal portion is arranged sequentially and the hot spot is imaged.

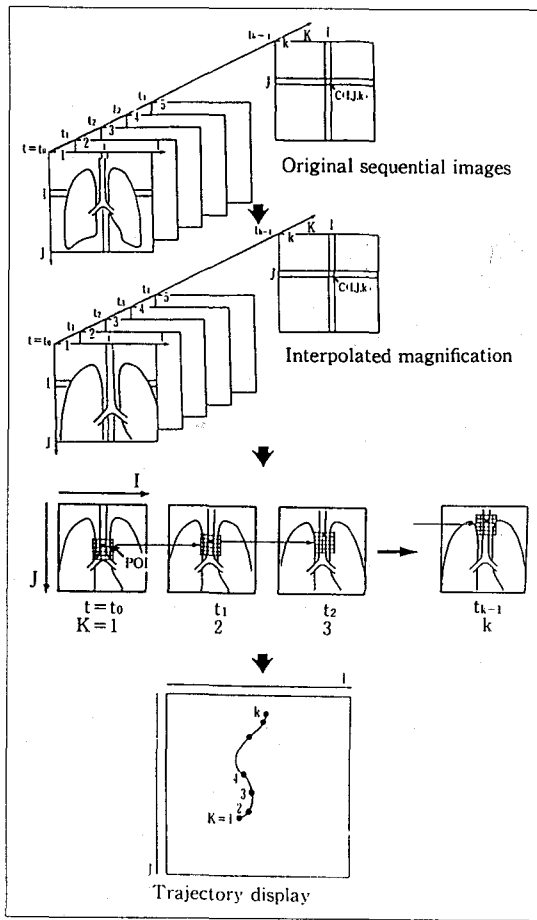


Fig. 3. Diagram showing the principle of the trajectory mode. The location of the point of interest (POI) is sequentially determined frame by frame and each mathematical location is connected using a B spline function.

Table 2. Definition of Indexes

Effective Transport Velocity; $V_{eff}=S/T$
Apparent Transport Velocity; $V_{app}=s/T$
Traveling Pathway Index; $\alpha =s/S$
Stasis Ratio ; $SR=\sum(\text{number of time}(\Delta si=0))/N$

nearly a standstill, a horizontal line is depicted. With radioaerosol inhalation, wide bands of trajectories are depicted<sup>18)</sup>.

## 2) Trajectory Mode

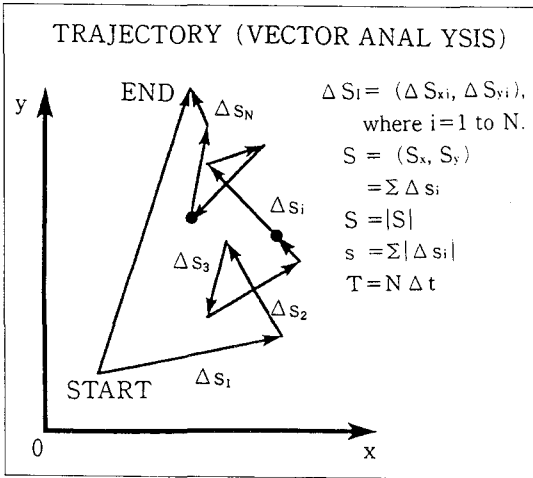
In order to analyze the transport of a mucous glob more accurately and quantitatively, the following method was devised and named "trajectory mode"<sup>18)</sup>.

At first a point of interest (POI) is set at a "Hot spot" on a frame data that was magnified from the original  $64 \times 64$  matrix data by interpolation, and its location mathematically determined and recorded in a computer. On the next frame, also similarly magnified by interpolation, the mathematically changed location of the same spot is measured and recorded. This procedure is repeated frame by frame and each mathematical location is connected using B spline function, which makes a trajectory of the transport of the hot spot (Fig. 3). This trajectory enables a detailed analysis of mucociliary transport on the trachea<sup>18)</sup>.

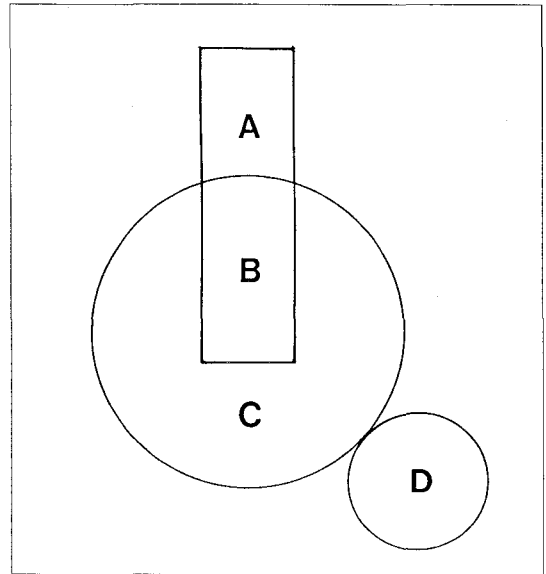
Using this trajectory, vector analysis is possible as shown in Fig. 4. Various parameters can be calculated using various values indicated in Table 2. For example, effective velocity ( $V_{eff}$ ) and apparent velocity ( $V_{app}$ ) of tracheal mucous transport in normal non-smokers, smokers and patients with chronic obstructive pulmonary disease (COPD) were as shown in Fig. 5. Fractions of forward transport, backward transport and stasis in mucous transport could also be easily calculated. Stasis ratios significantly differ between healthy smoker, nonsmokers, and patients with COPD with the latter the greatest.

## 2. Ciliated Airways in Lung Parenchyma

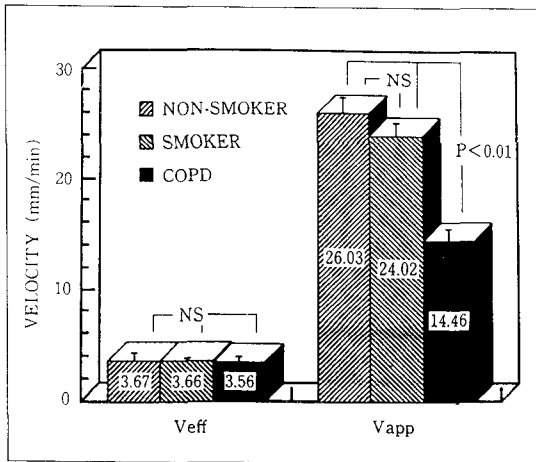
When radioaerosol is inhaled, radioactivity deposits in the extrapulmonary ciliated airways (A), intrapulmonary ciliated airways (B), in the non-ciliated small airways including the alveolar space (C), and in the esophagus and the stomach or the gastrointestinal (GI) tract (D) as illustrated in Fig.



**Fig. 4.** Vector analysis of a trajectory. From START to END the actual pathway is comprised of S1, S2, ...SN, although macroscopically it looks like a straight line between START and END. Each S1, S2, ...SN, is a vector and mathematical calculation is possible.



**Fig. 6.** Diagram of deposition sites of inhaled aerosol such as A, the trachea and the proximal portions of the major bronchi; B, the intrapulmonary ciliated airway; C, the non-ciliated small airways including the alveolar space; and D, the digestive canal like the mouth, the esophagus, the stomach, etc.



**Fig. 5.** Although there is no statistically significant difference in effective velocity (V<sub>eff</sub>) between nonsmokers, smokers and patients with chronic obstructive pulmonary disease (COPD), apparent velocity (V<sub>app</sub>) significantly differs between normal subjects (smokers and nonsmokers) and patients with COPD.

zero or immediately after aerosol inhalation is finished can be written as follows;

$$A_0 + B_0 + C_0 = T_0 \tag{1}$$

Where A, B, C represents the compartments in Fig. 5 and T, the total radioactivity in all three compartments. At time t, radioactivity at each compartment would be

$$A_t + B_t + C_t = T_t \tag{2}$$

If radioactivity is corrected for physical decay, the formula (2) becomes

$$A_{tc} + B_{tc} + C_{tc} = T_{tc} \tag{3}$$

If we define that the radioactivity remaining in the lung at 24 hrs later is the amount of radioactivity deposited in the non-ciliated space of the lung, C<sub>0</sub>, corrected for physical decay should be the same with C<sub>tc</sub>. C<sub>0</sub> = C<sub>tc</sub>.

Practically speaking, it is extremely difficult to

6<sup>12,13</sup>.

Disregarding the radioactivity in the stomach and/or the GI tract (D), the radioactivity at time

measure At without contamination by radioactivity in the esophagus behind the trachea that been swallowed. In evaluating the disappearance of radioactivity with time from the lung parenchyma that is nothing less than mucociliary clearance in the intrapulmonary ciliated airways, only radioactivity in the extrapulmonary airways should be taken into consideration. Radioactivity in the compartment A should be excluded from consideration. Thus the above formulae should be rewritten as follows;

$$B_0 + C_0 = T_0 \quad (1)$$

$$B_t + C_t = T_t \quad (2)$$

$$B_{tc} + C_{tc} = T_{tc} \quad (3)$$

Sequential measurements of radioactivity in the lung parenchyma or in the thorax excluding the extrapulmonary mediastinal region and the radioactivity in the same lung parenchyma at 24 hrs are only required to calculate the following indices;

#### Lung Retention Ratio (LRR)

$$LRR (\%) = T_{tc}/T_0 \times 100$$

This ratio expresses the amount of radioactivity remaining in the lungs at time t relative to the total radioactivity initially deposited.

#### Airway Deposition Ratio (ADR)

$$ADR (\%) = B_{tc}/T_0 \times 100 = (T_{tc} - C_0)/T_0 \times 100$$

ADR indicates the amount of radioactivity throughout the ciliated airways relative to the total radioactivity initially deposited in the lungs.

#### Airway Retention Ratio (ARR)

$$ARR (\%) = B_{tc}/B_0 \times 100 = \{(T_0 - T_{tc})/(T_0 - C_0)\} \times 100$$

ARR indicates what percentage of radioactivity initially deposited on the ciliated airways still remains there at time t.

#### Airway Clearance Efficiency (ACE)

$$ACE (\%) = (B_0 - B_{tc})/B_0 \times 100 \\ = \{(T_0 - T_{tc})/(T_0 - C_0)\} \times 100$$

ACE indicates what percentage of the radioactivity initially deposited on the ciliated airways has already been cleared by time t.

#### Alveolar Deposition Ratio (ALDR)

$$ALDR (\%) = C_0/T_0 \times 100$$

ALDR indicates the percentage of the total initial radioactivity remaining in the lung parenchyma at 24 hrs, or the percentage of radioactivity deposited in the nonciliated space of the lungs including the alveolar space at the completion of aerosol inhalation. The compartment C lack mucociliary clearance.

Normal values using human serum albumin aerosol the AMAD (activity median aerodynamic diameter) of which is 1.9 micron meter ( $\mu\text{m}$ ) with geometric standard deviation of 1.7 are published<sup>19)</sup>. The ALDR values could be different when different sized aerosols are inhaled. The smaller the aerosol size, the greater the ALDR<sup>16)</sup>. It is ideal to establish the normal ranges of each parameter at each laboratory according to the aerosols used.

## Mucociliary Clearance in Health and Disease

### 1. Large airways: Trachea and Major Bronchi

#### 1) Normal Subjects

In non-smoking normal subjects the transport of inhaled radioaerosol deposited in the airways is always axial and cephalad in direction, and steady and constant in its transport velocity, showing no stagnation of radioactivity in the trachea or the bronchi. However, in smokers and some of ex-smokers, although radioactive transport is still cephalad in direction and transport velocity nearly



constant, temporary collection of radioactivity is seen over the bronchi near or over the carina<sup>12)</sup>. Such stasis, however, never persists long. There is no visible retrograde transport or retreat, stasis or stagnation of mucous globs, frequent up-and-down motions of radioactive globs in the trachea or bronchi or migration into the other regions of the same lung or into the bronchus of the opposite lung or straying which are often observed in patients with obstructive airways disease<sup>13)</sup>.

However, the trajectory in normal subjects is tortuous and not a simple trajectory, which indicates that there is microscopically mixed forward and retrograde transports mixed with stasis but that the overall transport direction is toward the oropharynx<sup>18)</sup>.

## 2) Obstructive Airways Disease

Transport of radioactivity over the trachea and the major bronchi is extremely protean in its direction and transport patterns. As illustrated in Fig. 1, of 21 patients with obstructive airways disease studied by radioaerosol inhalation lung cine-scintigraphy, 14 showed temporary but frequent stopping and starting of radioactivity in the airways in the course of lung clearance.

Even after radioactivity begins to migrate up the trachea, it tends to stop on the way. Thus stopping and renewed migration were repeated many times in the course of mucous transport. Migration was often accelerated by coughing and/or clearing the throat, with the radioactive mucus finally swallowed into the stomach or expectorated. Sometimes radioactivity remains at the same spot without migration until cleared by coughing. In this sense cough appears to be the only means of upward propulsion of the mucus. In 10 there was reversal of mucus flow, in 5 migration or straying of radioactivity from one bronchus to that of the opposite lung, bypassing the trachea, followed by

shuttling between the right and left main bronchus, finally the mucus was coughed up. In 4 cases there was spiral or zigzag transport of radioactivity as shown in Fig. 1.

In another series of patients with obstructive airways disease not only was there shuttling of mucus between the right and left main bronchus, but there was also migration of mucus from one region of the lung into the different regions of the same lung frequently observed by radioaerosol inhalation lung cine-scintigraphy<sup>13)</sup>.

By trajectory mode analysis, the trajectory in patients with COPD is simpler in shape than that in normal subjects because the stasis ratio becomes higher<sup>18)</sup>.

## 3) Bronchiectasis

In bronchiectatic lung regions, deposition of inhaled radioaerosols is diminished and inhomogeneous. Radioaerosol inhalation lung cine-scintigraphy has revealed that transport of inhaled radioactivity from the bronchiectatic regions is greatly deranged. Regional stasis was observed in 12 of the 20 patients studied (12/20), regurgitation or reversed transport in 14/20, straying in 8/20, spiral or zigzag motion in 1/20. The transport patterns were more or less the combinations of these 4 basic abnormal transport patterns. When coughs occur, regurgitation and straying become more marked in the bronchiectatic regions. Only coughs can squeeze out radioactive mucus from inside the bronchiectatic regions to outside. Mucociliary clearance from the bronchiectatic regions is very inefficient without the help of coughing. These regional abnormalities in mucociliary transport seem to be responsible for the development of infections and hemoptysis in the bronchiectatic regions<sup>20)</sup>.

#### 4) Bronchogenic Carcinoma

In bronchogenic carcinoma, abnormal mucociliary transport patterns such as regurgitation, straying, stasis, and spiral or zigzag motions are seen especially when obstructive airways disease complicates bronchogenic carcinoma. Abnormal mucous transport patterns have nothing to do with histological diagnosis of bronchogenic carcinoma but with the degrees of functional and anatomical airways obstruction.

Bronchial invasion or protrusion of cancer in the large airways is often recongnized as "hot spots" which persists or disappear over time according to the degree of mucosal damage. When a tumor is covered with intact ciliary mucosa, the hot spots disappear with time, but it persists there when the bronchial mucus is denuded by the tumor<sup>21)</sup>.

#### 5) Idiopathic Interstitial Fibrosis and Pulmonary Vascular Disease

Transport on the large airways is not different from normal subjects unless complicated with obstructive airways disease. If complicated with COPD, similar transport patterns to those encountered in patients with COPD are observed<sup>22,23)</sup>.

### 2. Ciliated Airways in Lung Parenchyma

#### 1) Normal Subjects

The lung retention ratio (LRR) at 30, 60 and 90 min is in the range of 85-90, 80-85, and 75-80%, respectively. The alveolar deposition ratio (ALDR) is equivalent to the LRR at 24 hrs and amounts to about 40%. The airway deposition ratio (ADR) immediately after inhalation is finished is about 60% and decreases with time to 50, 45, and 40% at 30, 60 and 90 min, respectively. The airway retention ratio (APR) is in the range of 80-85, 65-70, 60-65% at 30, 60 and 90 min respectively. The ACE is in the range of 15-20, 30-35, 35-40%

at 30, 60 and 90 min, respectively. Normal smokers show a slightly faster clearance than non-smokers<sup>19)</sup>. The ALDR's are significantly larger in normal non-smoker than in normal smokers.

#### 2) Obstructive Airways Disease

The LRR itself is not distinguishable from the normal range, but the ALDR is significantly less than normal range. Both the ADR and the ARR are higher and the ACC less than the normal range, indicating that a larger fraction of inhaled aerosol deposits in the ciliated airways and that mucociliary clearance is less efficient<sup>13)</sup>.

#### 3) Idiopathic Interstitial Fibrosis and Pulmonary Vascular Disease

All the parameters remain in the normal range in idiopathic interstitial fibrosis<sup>22)</sup> and also not deranged from the normal range in pulmonary vascular diseases like pulmonary embolism or pulmonary vascular anomalies<sup>23)</sup>.

### Pharmacological Effects

Clinical effects of mucolytic agents and bronchodilators have been evaluated rather subjectively on the basic of patients' sense of clinical improvement. Quantitative evaluation seems possible applying the present methodology of radioaerosol inhalation and subsequent sequential imaging and measurement of radioactivity of the lungs. Reports regarding the drug effects as far are rather conflicting<sup>24-27)</sup>.

#### 1. Bromhexine

Bromhexine is claimed to liquefy mucus by breaking the muco-polysaccharide chains in the mucus, facilitating its removal. Giving Airway Clearance Efficiency (ACE) was evaluated by radioaerosol inhalation lung scintigraphy in 10 pati-

ents with various chest disease before and after 7 days of administration of 8 mg of bromhexine orally three time a day (t.i.d.). ACE was statistically barely significantly improved by chi-square test ( $p=0.05$ ). Pulmonary function test revealed little change before and after the administration except for maximum mid-expiratory flow rate (MMF) becoming slightly larger and RV/TLC ratio or (residual volume)/(total lung capacity) slightly smaller<sup>28)</sup>.

## 2. Beta 2-Stimulators

It is known that ciliary beat frequency in vitro becomes increased by administration of salbutamol<sup>29)</sup>. Administration of oral salbutamol 8 mg t.i.d. for 7 days did not change either radioaerosol inhalation lung images or quantitative parameters as compared with before administration, although significant bronchodilation occurred by pulmonary function test (PFT) after the 7 days of administration<sup>30)</sup>.

In the midst of radioactive measurement following radioaerosol inhalation a beta 2-stimulator procaterol was inhaled to see if there was any change in shape of the time-activity curve following drug administration. If the time-activity curve over the lungs becomes steeper, we could surmise that the mucociliary clearance was accelerated by the medication.

There was neither significant acceleration in mucous transport by radioaerosol inhalation lung cine-scintigraphy nor significant changes in the slope of time-activity curves. No changes were observed in any quantitative parameters after the drug administration in patients with bronchial asthma in remission, although spirometry indicated significant bronchodilation<sup>31)</sup>.

## 3. Aminophylline and Beta 2-Stimulator

Radioaerosol inhalation lung cine-scintigraphy

and PFT were performed on 10 patients with bronchial asthma in remission before and after 250 mg of aminophylline infusion followed by inhalation of salbutamol.

The bronchodilating effect of the combined treatment was significant; inhaled aerosol deposited more homogeneously and less centrally in the lungs. The penetration index increased from  $31 \pm 3\%$  to  $49 \pm 7\%$  and the alveolar deposition ratio from  $29 \pm 2\%$  to  $39 \pm 1\%$ . The ADR decreased from  $72 \pm 2\%$  to  $61 \pm 1\%$  immediately after the treatment. Spirometry indicated significant bronchodilation. However, there was little qualitative or quantitative improvement in mucociliary clearance after the treatment<sup>32)</sup>.

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