Radioaerosol Inhalation Lung Cine-Scintigraphy: a Preliminary Report

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ISAWA, T., TESHIMA, T., HIRANO, T., EBINA, A. and KONNO, K. *Radioaerosol Inhalation Lung Cine-Scintigraphy: a Preliminary Report*. Tohoku J. exp. Med., 1981, **134** (3), 245–255 — “Radioaerosol inhalation lung cine-scintigraphy”, a cinematographic display of the lungs following radioaerosol inhalation has been found to be extremely helpful not only to the visual assessment of mucociliary clearance in the lungs but also to the setting of regions of interest and to the interpretation and analysis of clearance curves over the regions of interest in the lungs. It is expected that this procedure offers an important means to the study of mucociliary clearance in health and disease in man. — aerosol; cine-scintigraphy; inhalation; lung; mucociliary clearance

Mucociliary activity can be assessed by sequential measurement of a tracer material placed on the airway whether the tracer be a radioactive droplet (Marin and Morrow 1969; Giordano and Holsclaw 1976; Isawa et al. 1980), teflon discs (Sackner et al. 1973; Wanner et al. 1973; Santz Cruz et al. 1974; Landa et al. 1975; Friedman et al. 1977; Goodman et al. 1977), or inhaled radioactive particles (Taplin and Poe 1965; Morrow et al. 1967; Isawa et al. 1970; Albert et al. 1973). Acute exposure to cigarette smoke, for example, could almost lead to ciliostasis in a dose-dependent manner in the dog trachea (Isawa et al. 1980), and no mucociliary clearance was demonstrated in two patients with Kartagener's syndrome (Camner et al. 1975).

Mucociliary clearance has been studied directly by bronchoscopy (Hilding 1957) or cine-bronchofiberscopy (Sackner et al. 1973; Wanner et al. 1973; Landa et al. 1975), or indirectly by radiography (Friedman et al. 1977) or external measurement of radioactivity by scintillation detectors including gamma cameras (Marin and Morrow 1969; Isawa et al. 1970, 1980; Sakakura and Proctor 1972; Yeates et al. 1975; Giordano and Holsclaw 1976).

We used to take sequential images of the lungs following radioaerosol inhalation for several hr to estimate mucociliary clearance (Isawa et al. 1970), but its

Received for publication, August 16, 1980.

Supported in part by Cancer Research Grant No. 101513 from the Ministry of Education, Science and Culture, Japan and a grant-in-aid from the Daiichi Radioisotope Laboratories, Ltd.

drawback was that the movement of radioactivity between one measurement to the next was not known and that exact positioning of the patient at each measurement was difficult. We have found that "cine-scintigraphy" of the lungs following radioaerosol inhalation is extremely helpful not only to the visual assessment of mucociliary clearance but also to the setting of regions of interest in the lungs and to the interpretation and analysis of clearance curves over the regions of interest.

The purpose of this paper is to describe our present method of studying mucociliary clearance of the lungs which we call "radioaerosol inhalation lung cine-scintigraphy" for a wider usage to explore mucociliary clearance mechanism in the lungs, a potentially important non-respiratory function of the lungs.

MATERIALS AND METHODS

Thirty patients with bronchogenic carcinoma, obstructive lung disease such as pulmonary emphysema and/or chronic bronchitis, bronchiectasis and seven normal volunteers were studied by the following method.

Immediately after inhaling ultrasonically generated (Mistogen EN-142; Mistogen Equipment Co., Calif., USA) ^{99m}Tc -human serum albumin aerosol (mass median diameter, $3.73\ \mu\text{m}$ and geometric standard deviation, 1.73 (Teshima et al. 1980)) in less than 2 min with tidal breathing through a mouth-piece with the nose clipped, the subject lay supine on the bed under a gamma camera (RC-IC-1205; Hitachi Medical Corporation, Tokyo, Japan) and radioactivity was measured over the thorax including the trachea generally for 2 hr continuously and at the 3rd hr again. The total radioactivity deposited in the thorax was from 1.5 to 2.0 mCi. Each 10 sec data in the matrices of 64×64 was fed into a computer (Hitachi EDR-4200 HD; Hitachi Medical Corporation, Tokyo, Japan) to make an image of the thorax. Each frame of the 10 sec data was retrieved and displayed in color cinematographically on the T.V. screen at the rate of 18 frames per sec and was also photographed by an 8 mm movie camera (Elmo 612 S-XL; Elmo Mfg. Corporation, Tokyo, Japan) at the same rate. We called this cinematographic display of the continuous measurement of inhaled radioaerosol "radioaerosol inhalation lung cine-scintigraphy" instead of "radioaerosol inhalation lung scintigraphy or imaging" (Taplin and Poe 1965; Isawa et al. 1970).

Seven regions of interest (ROI) were selected; they were in general over a perihilar region covering the large airways (ROI 1), a peripheral lung region (ROI 3), an intermediate lung region (ROI 2) between the ROI 1 and the ROI 3, the carina (ROI 4), the trachea (ROI 5), the whole right lung (ROI 6), and the whole left lung (ROI 7). Either the ROI 2 or the ROI 4 was often assigned to a different area of interest such as an area of excessive aerosol deposition when present. Time-activity curves or clearance curves were drawn by the computer for each area of interest after correcting physical half-life. Mucous velocity over the airways including the trachea was assessed by comparing the movement of radioactivity as a lump over an ROI with that over a more distal ROI.

RESULTS

Fig. 1 illustrates an inhalation lung image of the initial 60 sec of a normal volunteer, 29 year-old non-smoker who was made to hyperventilate several times during aerosol inhalation. The ROI's were selected as illustrated, and their clearance curves were as shown in Fig. 2. Cine-scintigraphy didn't show any evidence of abnormally prolonged retention of radioactivity on the airways or any

Fig. 1. Aerosol inhalation lung image (anterior view) of a 29 year old male non-smoker in the supine position with the numbered ROI's selected. Radioactivity in the initial 60 sec was integrated to make this image.

sudden change of radioactivity on the clearance curves with time in any of the ROI's. Not only clearance from the right lung (ROI 6) and the left lung (ROI 7) separately but both lungs as a whole (ROI (6+7)) was also assessed.

Fig. 3 is an initial 60 sec aerosol inhalation lung image of a 59-year-old man with pulmonary emphysema. He was also a 26 pack-year smoker. The forced vital capacity (FVC) was 1400 ml (47% of the predicted), and the forced expiratory volume in one sec ($FEV_{1.0\%}$) was 27%. Inhaled aerosol tended to deposit on the central large airways (Isawa et al. 1970). Cine-scintigraphy showed an extremely slow movement or near-stasis of radioactivity over the airways before it was triggered to move and partially expectorated by coughing or clearing throat (hawking). Fig. 4 showed step-like clearance curves at most ROI's except over the lung periphery (ROI 3) where radioactivity remained almost constant with time. At each step of clearance curves over the intrapulmonary airways such as in the ROI's 1, 2 and 4, radioactivity gradually increased with time or was crescendo in shape before it suddenly decreased by coughing or hawking. Radioactivity over the trachea (ROI 5) was reciprocal in phase as compared with those over the ROI's 1, 2 and 4.

Fig. 5 is an initial 60 sec image of a 64-year-old woman whose right middle lobe was resected en bloc with the intermediate bronchus for bronchogenic carcinoma and the remaining proximal portion of the intermediate bronchus was anastomosed with the right lower lobe bronchus six weeks previously; the so-called sleeve resec-

Fig. 2. Clearance curves over the ROI's indicated in Fig. 1. Ordinate: counts per sec (cps) per ROI. Abscissa: time in min. ROI 1, right perihilar region; ROI 2, intermediate lung region; ROI 3, peripheral lung region; ROI 4, carina; ROI 5, trachea; ROI 6, right whole lung; ROI 7, left whole lung; and ROI (6+7), both right and left lungs.

Fig. 3. Aerosol inhalation lung image (anterior view) of a 52-year-old male smoker with pulmonary emphysema in the supine position with the numbered ROI's. Radioactivity in the initial 60 sec was integrated to make this image.

tion was done. Inhaled aerosol tended to deposit on the central large airways. The ROI 1 was over the left perihilar region and the ROI 2 over the large airways including the site of anastomosis where excessive radioactivity deposited. Initially deposited radioactivity on the large airways in the left lung was cleared rapidly while radioactivity at the anastomotic site was cleared slowly. Clearance from the left lung was faster than that from the operated right lung as shown in Fig. 6. Clearance from the lung periphery was nearly stationary as shown in Fig. 7. The continuous 2 hr measurement was not feasible in this patient.

In bronchogenic carcinoma, excessive radioactivity deposited at the site of endotracheal or endobronchial prominence with cancer infiltration if airflow was maintained there and radioactivity at that site usually kept increasing with time before it was coughed up cephalad because radioactivity from the more distal lung regions was transported to accumulate there. Even after expectoration some excessive radioactivity remained at that site. When the trachea was included in the field of radiation therapy, excessive radioactivity once transported cephalad by coughing or hawking often retreated downward as far as the site of previous excessive radioactive accumulation.

In bronchiectasis, the amount of inhaled aerosol deposited was limited in the bronchiectatic regions and clearance from there was slow.

Fig. 4

Fig. 5. Aerosol inhalation lung image (anterior view) of a 64-year-old female with sleeve resection of the right middle lobe for bronchogenic carcinoma in the supine position with the numbered ROI's selected. Radioactivity in the initial 60 sec was integrated to make this image.

DISCUSSION

When a clearance curve over the large airways shows a rapid decline followed by a delayed peak formation over a more proximal region, it indicates clearance of aerosol as a lump (Fig. 6), but near-flat or horizontal clearance curves over the non-peripheral ROI's indicate that the input of the flow-in of radioactivity from more distal lung regions is in equilibrium with the output or mucous transport from the ROI's. When a clearance curve in the peripheral ROI shows a near-flat or horizontal one, what is meant by the near-flat curve is different from that over the non-peripheral ROI. The near-flat clearance curve in the lung periphery indicates that most inhaled aerosol has deposited in the non-ciliated bronchioles or the alveoli where mucociliary clearance is virtually absent or extremely slow (Albert et al. 1969). Measurement of mucous transport rate over the trachea is easy in

Fig. 4. Clearance curves over the ROI's indicated in Fig. 3. ROI 1, right perihilar region; ROI 2, intermediate lung region; ROI 3, peripheral lung region; ROI 4, a region of excessive radioactive deposition in the ROI 1; ROI 5, trachea; ROI 6, right whole lung; ROI 7, left whole lung; and ROI (6+7), both right and left lungs. Note the step-like clearance curves in all ROI's selected but in the ROI 3, peripheral lung region where radioactivity is near-horizontal. The sudden reduction of radioactivity in the ROI's 1, 2, 4, 6, 7, and (6+7) and the sudden rise in the ROI 5 coincided with coughing or hawking.

Fig. 6. Clearance curves over the ROI's indicated in Fig. 5. ROI 1, left perihilar region; ROI 2, right perihilar region including the site of bronchial anastomosis; ROI 4, carina; ROI 5, trachea; ROI 6, right whole lung; ROI 7, left whole lung; and ROI (6+7), both right and left lungs.

Fig. 7. Clearance curves over the ROI 1 (left perihilar region) and the ROI 3 (left peripheral lung region) indicated in Fig. 5. Measurement of radioactivity for one hr instead of 2 hr could also give a good idea of clearance of inhaled aerosol.

patients who more or less tends to show a preponderance of aerosol deposition on the central large airways if markers are placed at appropriate positions. We usually put them at the level of the midplane between the anterior and the posterior chest walls to simulate the *in vivo* location of the trachea and the major airways. Even in normal persons in whom inhaled aerosol doesn't show any preponderant deposition on the larger airways with tidal breathing, if he or she inhales aerosol with a hyperpneic maneuver for a short while, say, five or ten breaths, inhaled aerosol during the hyperpneic maneuver tends to deposit more on the larger airways, and we can assess mucous transport rate on the trachea either on cine-scintigraphy or on clearance curves. Furthermore, clearance from the right and left lungs is often different from each other. The patient illustrated in Fig. 5 was an example to show a difference in clearance between the non-operated lung and the operated lung. Although it is reported that simple transection of a major airway only temporarily decreases mucociliary clearance in the lungs, (Edmunds et al. 1969; Brody et al. 1972; Morinari et al. 1974) the patient under study (Fig. 5) definitely showed slowing of mucociliary clearance even 6 weeks after the so-called sleeve resection.

Importance of coughing or hawking in mucociliary clearance in patients with obstructive lung diseases, bronchogenic carcinoma or bronchiectasis was well appreciated both by radioaerosol inhalation lung cine-scintigraphy and by clearance curves as were shown in Fig. 3. The slow rise of radioactivity over the large airways (ROI's 1, 2 and 4) and the reciprocal slow declines over the trachea (ROI 5) would indicate impairment in mucous transport either due to the presence of too viscous mucus (Dulfano et al. 1971) or due to a decrease in both the number of the ciliated cells and the mean ciliary length in the large airways (Serafini and Michealson 1977). Downward retreat of once detached radioactivity cephalad by coughing or hawking seen in patients with bronchogenic carcinoma complicated with obstructive lung diseases under radiation therapy would also indicate similar impairment in mucous transport at the irradiated site (Fujiwara et al. 1972; Baldetorp et al. 1976). These findings were quite different from those with bronchogenic carcinoma without obstructive lung diseases or radiation therapy in that slowing of mucous transport or accumulation of radioactivity occurred only locally at the site of endotracheal or endobronchial carcinomatous infiltration or prominence. In this sense the presence of chronic obstructive lung diseases does seem to impair mucociliary clearance synergistically.

Even a possible spiral motion of radioactivity on the trachea or migration of radioactivity into the opposite bronchus after overriding the carina could often be appreciated on radioaerosol inhalation lung cine-scintigraphy, although mucous transport from the tracheobronchial tree is cephalad in direction as a rule. Thus under any situations, coughing or hawking seems to play an important role in the elimination of respiratory secretions and inhaled particles from the tracheobronchial tree.

Without the help of cine-scintigraphy mere clearance curves over the trachea

or near the midline of the thorax could even be misleading because radioactivity over a blindly set ROI might represent radioactivity in the esophagus, as radioactivity is swallowed down the esophagus after reaching the vocal cord unless it is coughed up. Therefore, aerosol inhalation lung cine-scintigraphy, or the cinematographic demonstration of the behavior of inhaled aerosol in the lungs seems to afford us an indispensable means to the accurate evaluation of mucociliary clearance in health and disease in man. Drawbacks of radioaerosol inhalation cine-scintigraphy are; 1) patient's cooperation is necessary, 2) a data storage and retrieval system is required. Even when patients are advised to void before radioactive measurement begins, some patients cannot keep lying supine for 2 hr because of physical urgencies. The patient illustrated in Fig. 5 was such case. To overcome these drawbacks, one hr measurement instead of 2 hr will do and a simple videotape system with a persistent scope attached to a gamma camera would give us the same information, although it takes time to edit cine-scintigraphy. The supine position is more comfortable to patients than the sitting position, and such device as a belt to fix the patient was not usually necessary.

To study mucociliary clearance mechanism which is one of non-respiratory functions of the lungs will surely contribute to the better understanding of lung function as a whole which has been taken as equivalent to measurement of only respiratory parameters such as lung volumes, mechanics, diffusion or arterial blood gases. Although definite clinicopathophysiologic significance of mucociliary clearance in health and disease is still at large (Wanner 1979), further investigations into this potentially important non-respiratory lung function and clarification of its real value in clinical medicine are to be awaited. Radioaerosol inhalation lung cine-scintigraphy would be an important methodology.

Acknowledgments

We thank Ms. Yuko Kobayashi for her clerical assistance in the preparation of the manuscript, the Ministry of Education, Science and Culture, Japan for installing the computer system (Hitachi EDR 4200 HD) for this study and Dr. Hiroshi Ogawa of the Daiichi Radioisotope Lab., Ltd., for his kind supply of human serum albumin solution for aerosol generation.

References

- 1) Albert, R.E., Lippmann, M. & Briscoe, W. (1969) The characteristics of bronchial clearance in humans and the effects of cigarette smoking. *Arch. environ. Health*, **18**, 738–755.
- 2) Albert, R.E., Lippmann, M., Peterson, H.T., Jr., Berger, J., Sanborn, K. & Bohning, D. (1973) Bronchial deposition and clearance of aerosols. *Arch. intern. Med.*, **131**, 115–127.
- 3) Baldetorp, L., Huberman, D., Håkansson, C.H. & Toremalm, N.G. (1976) Effects of ionizing radiation on the activity of the ciliated epithelium of the trachea. *Acta Radiol. (Ther)*, **15**, 225–232.
- 4) Brody, J.S., Klempfner, G., Staum, M.M., Vidyasagar, D., Kuhl, D.E. & Waldhausen, J.A. (1972) Mucociliary clearance after lung denervation and bronchial transection. *J. appl. Physiol.*, **32**, 160–164.

- 5) Camner, P., Mossberg, B. & Afzelius, B.A. (1975) Evidence for congenitally non-functioning cilia in the tracheobronchial tract in two subjects. *Amer. Rev. respir. Dis.*, **112**, 807-809.
- 6) Dulfano, M.J., Adler, K. & Philippoff, W. (1971) Sputum viscoelasticity in chronic bronchitis. *Amer. Rev. respir. Dis.*, **104**, 88-98.
- 7) Edmunds, L.H., Jr, Stallone, R.J., Graf, P.D., Sagel, S.S. & Greenspan, R.H. (1969) Mucus transport in transplanted lungs of dogs. *Surgery*, **66**, 15-22.
- 8) Friedman, M., Dougherty, R., Nelson, S.R., White, R.P., Sackner, M.A. & Wanner, A. (1977) Acute effects of an aerosol hair spray on tracheal mucociliary transport. *Amer. Rev. respir. Dis.*, **116**, 281-286.
- 9) Fujiwara, K., Håkansson, C.H. & Toremalm, N.G. (1972) Influence of ionizing radiation on ciliary cell activity in the respiratory tract. *Acta Radiol. (Ther)*, **11**, 513-520.
- 10) Giordano, A. & Holsclaw, D.S. (1976) Tracheal resection and mucociliary clearance. *Ann. Otol. Rhino. Laryngol.*, **85**, 631-639.
- 11) Goodman, R.M., Yergin, B.M., Landa, J.F., Golinvaux, M.H. & Sackner, M.A. (1977) Tracheal mucous velocity in non-smokers, smokers, and patients with obstructive lung disease. *Fed. Proc.*, **36**, 607. (abstract)
- 12) Hilding, A.C. (1957) Ciliary streaming in the bronchial tree and the time element in carcinogenesis. *New. Engl. J. Med.*, **256**, 634-640.
- 13) Isawa, T., Wasserman, K. & Taplin, G.V. (1970) Lung scintigraphy and pulmonary function studies in obstructive airway disease. *Amer. Rev. respir. Dis.*, **102**, 161-172.
- 14) Isawa, T., Hirano, T., Teshima, T. & Konno, K. (1980) Effect of non-filtered and filtered cigarette smoke on mucociliary clearance mechanism. *Tohoku J. exp. Med.*, **130**, 189-197.
- 15) Landa, J.F., Hirsch, J.A. & Lebeaux, M.I. (1975) Effects of topical and general anesthetic agents on tracheal mucous velocity of sheep. *J. appl. Physiol.*, **38**, 946-948.
- 16) Marin, M.G. & Morrow, P.E. (1969) Effect of changing inspired O₂ and CO₂ levels on tracheal mucociliary transport rate. *J. appl. Physiol.*, **27**, 385-388.
- 17) Morinari, H., Shimada, K., Taplin, G.V., Johnson, D.E. & Benfield, J.R. (1974) Bronchial mucus after lung autotransplantation in dogs. *J. thorac. cardiovasc. Surg.*, **67**, 484-490.
- 18) Morrow, P.E., Gibb, F.R. & Gazioglu, K.M. (1967) A study of particulate clearance from the human lungs. *Amer. Rev. respir. Dis.*, **96**, 1209-1221.
- 19) Sackner, M.A., Rosen, M.J. & Wanner, A. (1973) Estimation of tracheal mucous velocity by bronchofiberscopy. *J. appl. Physiol.*, **34**, 495-499.
- 20) Sakakura, Y. & Proctor, D.F. (1972) The effect of various conditions on tracheal mucociliary transport in dogs. *Proc. Soc. exp. Biol. Med.*, **140**, 870-879.
- 21) Santa Cruz, R., Landa, J.F., Hirsch, J. & Sackner, M.A. (1974) Tracheal mucous velocity in normal man and patients with obstructive lung disease; Effects of terbutaline. *Amer. Rev. respir. Dis.*, **109**, 458-463.
- 22) Serafini, S.M. & Michealson, E.D. (1977) Length and distribution of cilia in human and canine airways. *Bull. Physiopath. Respir. (Nancy)*, **13**, 551-559.
- 23) Taplin, G.V. & Poe, N.D. (1965) A dual lung scanning technique for evaluation of pulmonary function. *Radiology*, **85**, 365-368.
- 24) Teshima, T., Isawa, T., Hirano, T., Ebina, A. & Konno, K. (1980) Aerosol inhalation lung scan for evaluation of non-respiratory function. *Jap. J. thorac. Dis.*, **18**, 129. (abstract)
- 25) Wanner, A., Hirsch, J.A., Greenelch, D.E., Swenson, E.W. & Fore, T. (1973) Tracheal mucous velocity in beagles after chronic exposure to cigarette smoke. *Arch. environ. Health*, **27**, 370-371.
- 26) Wanner, A. (1979) Clinical aspects of mucociliary transport. *Amer. Rev. respir. Dis.*, **116**, 73-125.
- 27) Yeates D.B., Aspin, N., Levison, H., Jones, M.T. & Bryan, A.C. (1975) Mucociliary tracheal transport rates in man. *J. appl. Physiol.*, **39**, 487-495.