Assessment of Mucociliary Clearance in Patients with Tracheobronchoplasty Using Radioaerosol

Shigeru Kosuda, Atsushi Kubo, Toshikazu Sanmiya, Yoshiyuki Okano, Shozo Hashimoto, Takashi Suzuki, and Tsuneo Ishihara

Okura National Hospital and Keio University Hospital, Tokyo, Japan

To assess mucociliary clearance in patients with tracheobronchoplasty, radioaerosol inhalation scanning was performed in 14 patients. The unilateral total lung clearance curve was fitted into two compartmental curves, fast and slow, by least-squares techniques in order to assess mucociliary clearance of the bronchial tree quantitatively. Half-time ($T_{1/2}$) of the curve resulting from the subtraction of the slow compartment curve from the fast compartment curve was calculated. The mucociliary clearance of the bronchial tree post so-called lobectomy (N = 5) was intact ($T_{1/2}$; 13.1 ± 7.3 min). On the other hand, the mucociliary clearance of the bronchial tree postreconstruction (N = 14) was prolonged ($T_{1/2}$; 28.3 ± 10.6 min), compared with that of the control bronchial tree (N = 15, $T_{1/2}$; 11.9 ± 3.9 min) ($p < 0.01$). However, the mucociliary clearance of the bronchial tree postreconstruction showed improvement with the passage of time, and the original clearance was regained 5 to 12 mo after the operation. Radioaerosol inhalation studies revealed both the degree of impairment and the recovery time of mucociliary clearance in patients post-tracheobronchoplasty.

J Nucl Med 27:1397–1402, 1986

Progress in respiratory surgery has made it possible to resect and reconstruct safely every segment of the respiratory tract by end-to-end anastomosis. This technique, that is, tracheobronchoplasty or tracheobronchial reconstruction, preserves ipsilateral pulmonary parenchyma. Since tracheobronchoplasty for a patient with lung cancer was first described as sleeve lobectomy by Price-Thomas et al. (*1,2*), this technique has been performed on patients with lung cancers which infiltrate into the trachea or the large bronchus.

Most of the patients with tracheobronchoplasty lose the cough reaction and are unable to cough up phlegm on their own for a certain period after the operation. They often suffer from respiratory tract complications. Mucociliary transport in the airway is an important mechanism for the elimination of inhaled foreign materials and debris. It is well known that mucociliary transport is related to mucus production and to ciliary activity (*3*). It appears that both of these factors are impaired by this reconstructive surgery. No investigators have reported to what degree the mucociliary transport system is damaged by tracheobronchoplasty. In order to evaluate the effect of tracheobronchoplasty on mucociliary transport, we studied the clearance of inhaled radioaerosol from the bronchial trees of postoperative patients utilizing both visual and quantitative assessments.

MATERIALS AND METHODS

Our study group included 14 patients with lung cancer, 11 males and three females aged 31–71 yr (means 57.6), investigated at our institutions during a 7-mo period. Lung cancer was histologically proved to be squamous cell carcinoma in four patients; adenocarcinoma, three; large cell carcinoma, two; adenoid cystic carcinoma, two; and small cell carcinoma, mucoepidermoid carcinoma, and metastatic osteosarcoma, one each. We performed this study 11 days to 4-yr and 8-mo (mean 16.1 mo) after tracheobronchoplasty. Three patients underwent two consecutive studies. Another patient underwent this study after tracheobronchoplasty had been performed in both lungs, and one patient underwent carinal resection and received post-

Received Sept. 27, 1985; revision accepted Mar. 6, 1986.

For reprints contact: Shigeru Kosuda, MD, Dept. of Radiology, Okura National Hospital, 2-10-1 Okura Setagaya-ku, Tokyo 157, Japan.

operative irradiation to the upper mediastinum. The dose of the irradiation was 30 Gy.

On the basis of operative procedure, the subjects were divided into two groups: the reconstructive surgery group (nine cases) and the so-called lobectomy group (five cases). The reconstructive surgery group included three cases of sleeve lobectomy of the left lower lobe, two cases of sleeve lobectomy of the right upper lobe, two cases of sleeve lobectomy of the left upper lobe, one case of carinal resection, and one case of sleeve lobectomy of both the right upper lobe and the left anterior basal segment. The lobectomy group included cases of lobectomy of the right upper lobe, the right upper and middle lobes, the right lower lobe, the left upper lobe and the left lower lobe, respectively.

We used human serum albumin labeled with technetium-99m (^{99m}Tc) as radioaerosol. In order to produce aerosol particles, we used an ultrasonic nebulizer apparatus*. A mouthpiece with a three-way valve allowed aerosol inhalation. The subjects performed regular inhalation for 3 min at 25 breaths per minute through a short nozzle in a sitting position. We obtained anterior views of the chest with the patient supine, starting immediately after the inhalation and continuing for 120 min. Tracheobronchial imaging was performed with a gamma camera equipped with a low-energy parallel hole collimator and interfaced with a mini-computer system. The data were stored in a computer in frame mode in 64 × 64 matrix, each frame covering 60 sec. Each subject was inhibited from coughing or hacking and maintained with a normal pattern of respiration during data collection because cephalad migration of radioactivity was accelerated by both coughing and hacking on a normal control. All of the subjects abstained from expectorants for at least one day before radioaerosol inhalation studies.

The clearance of ^{99m}Tc albumin particles from the bronchial tree was estimated both by visual assessment of radioactivity transport using the cinemode of the computer system and by quantitative assessment of the clearance curve of each total lung. In order to evaluate the mucociliary clearance of the bronchial tree quantitatively, each total lung clearance curve was fitted into two compartmental curves, fast and slow, by least-squares techniques after correction for the physical decay of ^{99m}Tc, and both temporal and spatial smoothing. The half-time ($T_{1/2}$) of the curve resulting from the subtraction of the slow compartment curve from the fast compartment curve was calculated (Fig. 1). These $T_{1/2}$ values were considered to be measures of mucociliary clearance. In patients with tracheobronchoplasty, the site of anastomosis was included in the region of interest. All of the unoperated total lungs contralateral to the operated lungs were included in the control group. Chest radiography and perfusion lung imaging were done within a week of radioaerosol inhalation studies, but no abnormal findings were shown in the unoperated lungs.

RESULTS

Each unilateral total lung in our subjects was classified into one of three groups: Group A (control group) or total lung without surgical procedures (N = 15), Group B or postlobectomy (N = 5), and Group C or postreconstructive surgery (N = 14).

In the visual assessment of radioactivity transport

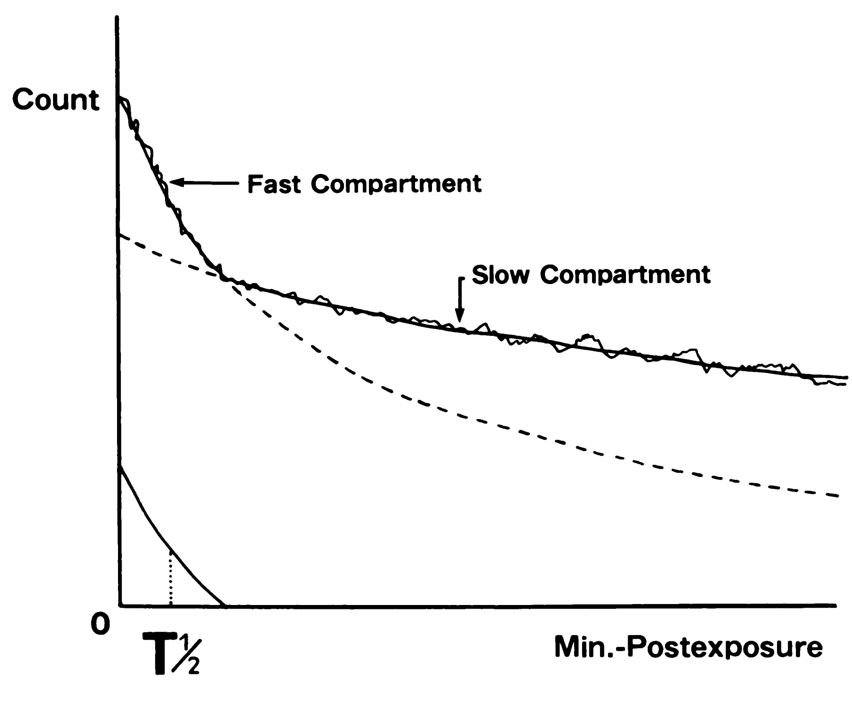

FIGURE 1
Original time-activity curve for unilateral total lung and its fitted curves, fast and slow compartments, derived from least-squares fit technique. $T_{1/2}$ is half time of curve resulting from subtraction of slow compartment curve from fast compartment curve

using the cinematographic display, both Group A and Group B showed steady and smooth cephalad migration of radioactivity toward the oropharyx. On the other hand, in Group C (the reconstructive group), nine out of 14 subjects (64.2%) showed sluggish migration of radioactivity across the site of anastomosis. Five out of 14 subjects (35.8%) showed stasis or retention of albumin particles at the site of anastomosis, whereas the migration of radioactivity in the distal airway was relatively smooth (Figs. 2A and 2B).

The values and distribution of $T_{1/2}$ from the quantitative analyses are shown in Fig. 3. All subjects in Group C (the reconstructive group) showed delayed mucociliary clearance as compared with Group A (the control group) ($p < 0.01$). In Group B (the so-called lobectomy group), although the clearance appeared to be slightly delayed as compared with Group A, this difference was not statistically significant. The value of $T_{1/2}$ coincided well with the visual assessment of radioactivity transport. All subjects with stasis of radioactivity clustered at the site of anastomosis had $T_{1/2}$ values greater than 30 min.

The relationship between the $T_{1/2}$ value and the number of months after tracheobronchoplasty is shown in Fig. 4. Mucociliary clearance is severely impaired just after tracheobronchoplasty, but gradually shows improvement. From the viewpoint of Fig. 4, the recovery time of mucociliary transport seems to be 5 to 12 mo. Figure 4 also suggests the probability that mucociliary clearance is damaged for a long time by irradiation.

DISCUSSION

Tracheobronchoplasty is becoming a standard operative technique for lung cancer because it provides the theoretical advantage of preserving functional lung without compromising the adequacy of tumor resection (*4*). However, patients with tracheobronchoplasty often suffer from respiratory tract complications at an early stage after the operation, such as the retention of the sputum and atelectasis in the distribution of the bronchus with the reconstructive surgery (*5,6*).

It is well known that mucociliary transport depends on numerous factors; ciliary activity, mucus production, differential airflow, etc. (*7*). The degree to which any of these factors alone influence mucociliary clearance of patients with tracheobronchoplasty remains to be clarified. We think our observation will have clinical relevance in that it identifies and quantitates a factor which contributes to making patients with tracheobronchoplasty vulnerable to postoperative complications. Therefore, it is crucial to assess the mucociliary clearance in patients who have undergone tracheobronchoplasty.

Radioaerosol inhalation scanning procedures are known to be a useful and noninvasive technique to evaluate mucociliary clearance. Technetium-99m albumin aerosol is an inert and nonpermeable substance to the pulmonary epithelium and we have never experienced increased background activity due to poor tagging of albumin. We believe that the physical integrity of the aerosol used in our study was excellent. Recently, radioaerosol inhalation scanning has been performed to assess mucociliary transport using radioaerosol inhalation lung cinescintigraphy by editing the data stored in a computer system into a cinematographic display. There are many reports of mucociliary clearance using radioaerosols in patients with obstructive airways disease (*9–12*). On the other hand, the mucociliary clearance mechanism in patients with respiratory surgery has not been studied extensively, although several canine studies have been reported (*13,14*).

Indices to quantify mucociliary clearance mechanisms in the lungs have not yet been determined. Some investigators have found it useful to measure the amount of bronchial deposition retained at a given time (*12,15,16*). However, the distribution of radioaerosol particle deposition in the lungs is influenced by many physical factors (*17,18*). Other investigators favor the measurement of the time (T_{50}) taken to clear 50% of the tracer particles deposited in the tracheobronchial tree (*19,20*). However, this measurement is also influenced by the distribution of tracer particle deposition. Physiologically, the disappearance of an inhaled substance from the pulmonary system is due to several mechanisms; not only mucociliary clearance, but also lymphatic or blood clearance (*21*), active or passive movement across the epithelium (*22*), alveolobronchial transport (*23*), and so on. Therefore, the clearance curve of the total lung invariably reflects these different rates of radioisotopic removal and the time course of radioactive measurements may be made more complex by rearrangements of radioactivity within the thoracic volume, as well as by multiple processes affecting clearance.

The kinetics of clearance of an inhaled substance can be formulated as an exponential expression. The radioaerosol clearance curve of the total lung consists of several multicompartment curves and is described as multiexponential expression (*24*),

$$X(t) = a\exp(-\lambda_1 t) + b\exp(-\lambda_2 t) + c\exp(-\lambda_3 t) + d\exp(-\lambda_4 t).$$

The mucociliary clearance velocity of the main bronchus, which is the principal factor in our study, is far faster than that of any of the other clearance systems. In particular, the clearance of ^{99m}Tc albumin particles from the alveoli is so slow that it may be dismissed as negligible for the first 2 hr. Therefore, we fitted the clearance curve of each total lung into two exponential curves which represent the fast and slow compartments.

The fast compartment seems to indicate mainly the mucociliary clearance of the main bronchus and the slow compartment is thought to indicate the aggregate of the other clearance systems because the clearance curve of total lung excepting the main bronchus almost coincided with the slow compartment curve we speculated. The $T_{1/2}$ of the curve resulting from the subtraction of the slow compartment curve from the fast

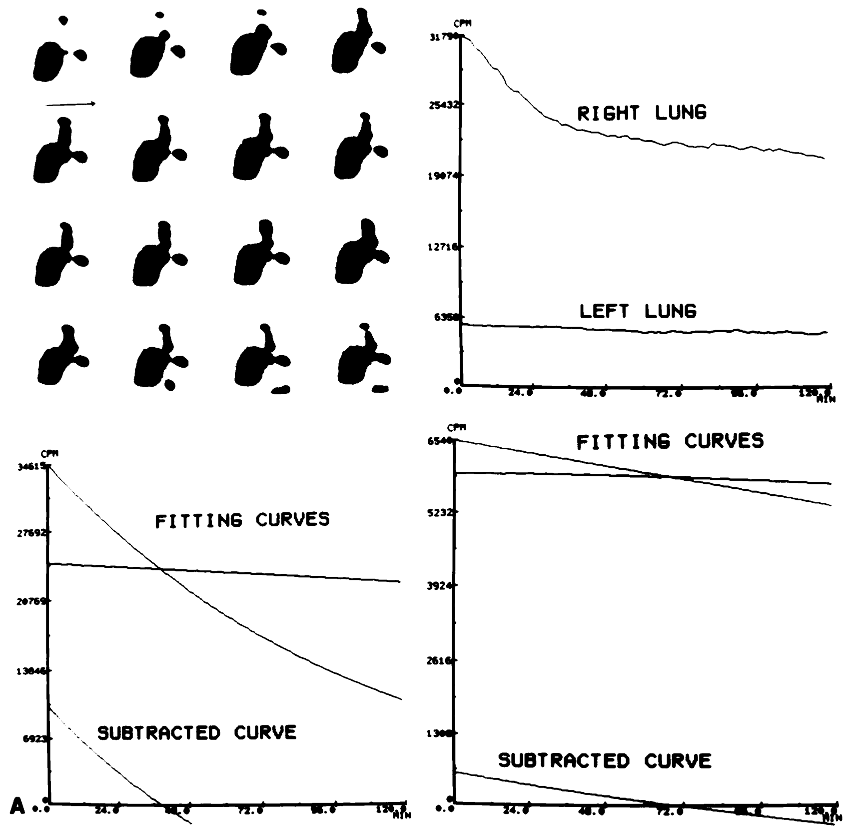

FIGURE 2A
63-yr-old male who underwent sleeve resection of left upper lobe because of pulmonary squamous cell carcinoma. Radioaerosol study was performed 39 days after reconstructive surgery. Upper left. 1-min lung images were made every 7 min after radioaerosol inhalation, progressing from upper left to lower right. Note stasis of radioactivity clustered at site of anastomosis, whereas steady migration of radioactivity toward oropharynx is seen in right, unoperated lung (right lung is toward viewer's left). Upper right. Original time-activity curves of right and left total lungs, respectively. Lower left: Fitted curves, fast and slow compartments, of right lung. $T_{1/2}$ of subtracted curve was 19 min. Lower right: Fitted curves of left lung. $T_{1/2}$ of subtracted curve was 34 min.

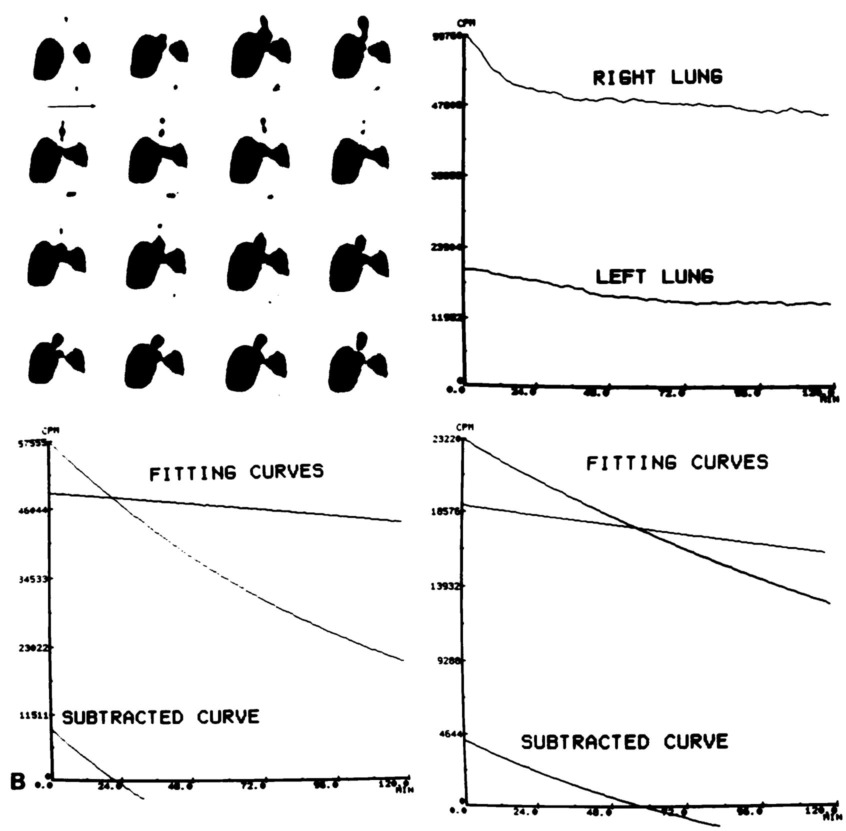

FIGURE 2B
Consecutive radioaerosol study in same patient performed 103 days after reconstructive surgery. Upper left: 1-min lung images reveal cephalad migration of radioactivity across site of anastomosis. Upper right: Original time-activity curves of respective total lungs. Lower left: Fitted curves, fast and slow compartments, of right lung. $T_{1/2}$ of subtracted curve was 10.5 min. Lower right: Fitted curves of left lung. $T_{1/2}$ of subtracted curve was 26 min, showing improvement of mucociliary transport in operated lung. At this time we observed no postoperative complications, such as proliferation of granuloma, degeneration or necrosis at site of anastomosis as determined by bronchoscopic examination

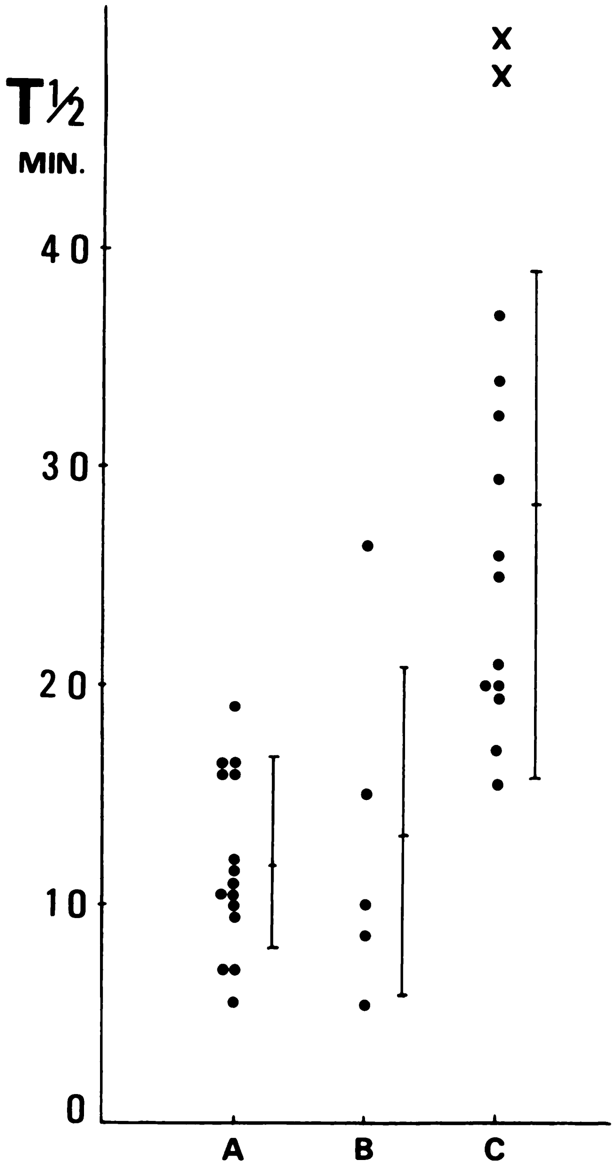

FIGURE 3
Distribution of $T_{1/2}$ values in three groups. Distribution of Group A (control), Group B (lobectomy), and group C (reconstruction group) were 11.9 ± 3.9 min (n = 15), 13.1 ± 7.3 min (n = 5), 28.3 ± 10.6 min (n = 14), respectively. (×) Lung that received postoperative irradiation

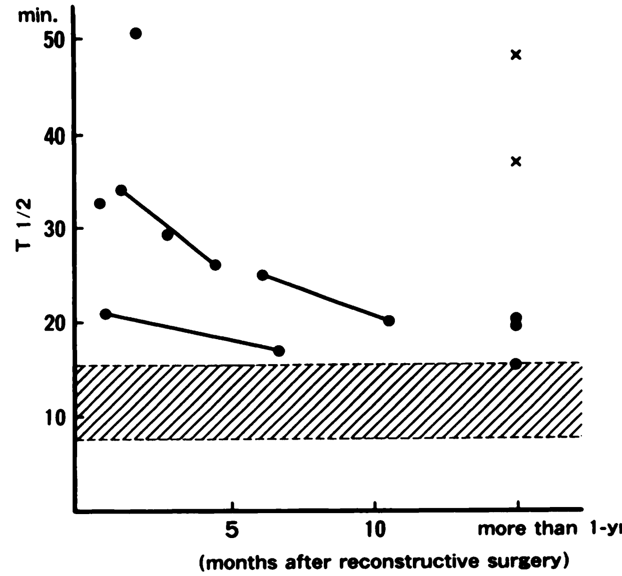

FIGURE 4
Relationship between $T_{1/2}$ value and months after tracheobronchoplasty. Shaded zone shows normal range of $T_{1/2}$ 11.9 ± 3.9 min. (×) lung that received postoperative irradiation. Lines connecting two points denotes consecutive studies on same patient

compartment curve is independent of the distribution of radioaerosol particles and is, therefore, suitable as an index to quatify the mucociliary clearance of the main bronchus.

In our study, the bronchial trees with tracheobronchoplasty showed delayed radionuclide clearance as compared with controls ($p < 0.01$), and markedly delayed radionuclide clearance was seen within the second postoperative month (Fig. 4). However, all of the mucociliary clearance curves of the bronchial trees with tracheobronchoplasty showed improvement with the passage of time, excluding one subject irradiated after the operation. There was no statistical difference between the bronchial trees post so-called lobectomy and the controls. These results were in agreement with the visual assessment by cinematographic display. Retention or stasis of radioactivity was observed at the site of anastomosis and this finding seemed to demonstrate the retention of the sputum at the anastomosis site.

Several factors are considered to be responsible for the prolongation of radionuclide clearance in the bronchial tree post-tracheobronchoplasty. We believe that at an early stage after the operation the most dominant factor to be considered is the defect of ciliated cells at the site of anastomosis. Following the destruction of epithelium by experimental trauma, a sequence of epithelial regeneration occurs: migration from adjacent epithelium, multiplication of undifferentiated cells, reorientation and differentiation. The time for complete regeneration of the mucosa ranges from a few days to several months after experimental trauma (*25,26*). There are only a few reports on the evaluation of function of the reconstructed tracheobronchial tract. It has been reported, on the basis of high speed cinebronchograms, that the original movement of the reconstructed respiratory tract is regained 6 mo after the operation (*5*). In our case (Fig. 4) the recovery time of mucociliary transport seems to be 5 to 12 mo, which is longer than that of experimental trauma or mechanical denudation. The reason is that the recovery time of mucociliary transport post-tracheobronchoplasty is significantly influenced by anastomotic complications, that is, the tension, decreased blood supply, the extent of the destructive lesion, and the presence of secondary bacterial infection at the site of anastomosis. At a later stage after the operation the dominant factor seems to be the proliferation of granuloma. The difference in diameter between the bronchial segment to be anastomosed is not negligible in sleeve lobectomy. The tension or deformity of bronchus at the anastomosed site is thought to influence the differential airflow mechanism. In addition, as a result of decreased blood supply, degeneration or necrosis in the bronchial wall is sometimes observed by bronchoscopic examination.

It goes without saying that mucociliary clearance depends not only on ciliary activity but also on mucus production and differential airflow mechanism. The mucus-secreting structures of the airways are impaired by denervation from 13 to 40 wk after surgery (*14*); however, ciliary action appears to be independent of nervous control (*27*). If mucociliary clearance does not show improvement by 12 mo after tracheobronchoplasty, excessive granuloma proliferation, tissue necrosis, or the recurrence of lung cancer should be suspected. In addition, irradiation effects and accompanying obstructive airway disease should be taken into consideration, although the effect of ionizing radiation on mucociliary clearance has not yet been reported in detail. None of our subjects showed severe pulmonary dysfunction before the operation (forced expiratory volume in 1 sec/% forced vital capacity, >50%; % predicted normal volume, >65%), nor had they any history of asthma.

In conclusion, radioaerosol inhalation studies are noninvasive and suitable for serial studies. $T_{1/2}$ values derived from fitting exponential curves to the data using least-squares techniques appears to be a relatively reliable means of assessing the impairment of mucociliary clearance in patients with tracheobronchoplasty.

FOOTNOTE

* DeVilbiss ultrasonic nebulizer apparatus (Model 65), Somerset, PA.

ACKNOWLEDGMENT

The authors thank Dr. Kenji Kawakami for the technical advice he provided.

REFERENCES

1. Price-Thomas C: Conservative resection of the bronchial tree. *J R Coll Surg Edin* 1:169–171, 1956
2. Paulson DL, Shaw RR: Bronchial anastomosis and bronchoplastic procedures in the interest of preservation of lung tissue. *J Thorac Cardiovasc Surg* 29:238–259, 1955
3. Kilburn KH: A hypothesis for pulmonary clearance and its implications. *Am Rev Resp Dis* 98:449–462, 1968
4. Weisel RD, Cooper JD, Delarue NC, et al: Sleeve lobectomy for carcinoma of the lung. *J Thorac Cardiovasc Surg* 78:839–849, 1979
5. Ishihara T, Ikeda T, Inoue H, et al: Resection of cancer of lung and carina. *J Thorac Cardiovasc Surg* 73:936–943, 1977
6. Naruke T, Yoneyama T, Ogata T, et al: Bronchoplastic procedure for lung cancer. *J Thorac Cardiovasc Surg* 73:927–935, 1977
7. Warwick WJ: Mechnisms of mucous transport. *Eur J Respir Dis* 64:162–167, 1983
8. Camner P, Mossberg B, Philipson K: Tracheobronchial clearance and chronic obstructive lung disease. *Scand J Respir Dis* 54:272–281, 1973
9. Santa Cruz R, Landa J, Hirsch J, et al: Tracheal mucus velocity in normal man and patients with obstructive lung disease; effects of terbutaline. *Am Rev Respir Dis* 109:458–463, 1974
10. Goodman RM, Yergin BM, Landa JF, et al: Relationship of smoking history and pulmonary function tests to tracheal mucous velocity in nonsmokers, young smokers, exsmokers, and patients with chronic bronchitis. *Am Rev Respir Dis* 117:205–214, 1978
11. Thomson ML, Short MD: Mucociliary function in health, chronic obstructive airway disease, and asbestosis. *J Appl Physiol* 26:535–539, 1969
12. Isawa T, Teshima T, Hirano T, et al: Lung clearance mechanisms in obstructive airways disease. *J Nucl Med* 25:447–454, 1984
13. Morinari H, Shimada K, Taplin GV, et al: Bronchial mucus after lung autoplantation in dogs. *J Thorac Cardiovasc Surg* 67:484–490, 1974
14. Brody JS, Klempfner G, Staum MM, et al: Mucociliary clearance after denervation and bronchial transection. *J Appl Physiol* 32:160–164, 1972
15. Thomson ML, Pavia D: Particle penetration and clearance in the human lung. *Arch Environ Health* 29:214–219, 1974
16. Albert RE, Lippman M, Peterson HT, et al: Bronchial deposition and clearance of aerosols. *Arch Intern Med* 131:115–128, 1973
17. Stuart BO: Deposition of inhaled aerosols. *Arch Intern Med* 131:60–72, 1973
18. Hounam RF, Morgan A: Particle deposition. In *Respiratory Defense Mechanisms*, Part I, Brain JD, Proctor DF, Reid LM, eds. New York and Basel, Marcel Dekker, Inc., 1977, pp 125–156
19. Pavia D: Lung mucociliary clearance. In *Aerosols and the Lung: Clinical and Experimental Aspects*, Clarke SW, Pavia D, eds. London, Butterworth & Co., Ltd., 1984. pp 127–155
20. Morrow PE, Gibb FR, Gazioglu KM: A study of particulate clearance from the human lungs. *Am Rev Respir Dis* 96:1209–1221, 1967
21. Morrow PE: Alveolar clearance of aerosols. *Arch Intern Med* 131:101–108, 1973
22. Minty BD, Jordan C, Lones JG: Rapid improvement in abnormal pulmonary epithelial permeability after stopping cigarettes. *Br Med J* 28:1183–1186, 1981
23. Green GM: Alveolobronchiolar transport mechanisms. *Arch Intern Med* 131:109–114, 1973
24. Morrow PE: Clearance kinetics of inhaled particles. In *Respiratory Defense Mechanisms*, Part I, Brain JD, Proctor DF, Reid LM, eds. New York and Basel, Marcel Dekker, Inc., 1977, pp 491–543
25. Battista SP, Denine EP, Kensler CJ: Restoration of tracheal mucosa and ciliary particle transport activity after mechanical denudation in the chicken. *Toxicol Appl Pharmacol* 22:59–69, 1972
26. Gorham CB, Bacher JA: Regeneration of the human maxillary antral lining. *Arch Otolaryngol* 11:763–771, 1930
27. Florey H, Carleton HM, Wells AQ: Mucus secretion in the trachea. *Br J Exptl Pathol* 13:269–284, 1932