Alveolar Integrity in Pulmonary Emphysema Using Technetium-99m-DTPA and Technetium-99m-HMPAO Radioaerosol Inhalation Lung Scintigraphy

Chia-Hung Kao, Rei-Chin Wang, Hui-Tzu Lin, Shu-Ling Yu, Shyh-Jen Wang and Chi-Der Chiang

Department of Nuclear Medicine and Division of Chest Medicine, Taichung Veterans General Hospital, Taichung, Taiwan, Republic of China

The alveolar integrity (AI) in 17 male patients with pulmonary emphysema (EMPH) diagnosed by chest x-ray was measured by ^{99m}Tc-DTPA and ^{99m}Tc-HMPAO radioaerosol inhalation lung scintigraphy. **Methods:** The patients were divided into two groups: (A) nine patients with pulmonary emphysema and normal carbon monoxide diffusion capacity (DLCO) and (B) eight patients with pulmonary emphysema and abnormal DLCO. The degree of AI damage in EMPH was presented as the slope of the time-activity curves from the dynamic left lung imagings in DTPA and HMPAO. The AI of EMPH patients were compared with the AI of 16 normal controls. **Results:** The results show that: (1) the slope of DTPA is larger than that of HMPAO in each of the portions of the left lung for any of the study groups; (2) statistical differences were found between the normal controls and EMPH patients in HMPAO but not in DTPA; and (3) the correlation was not good between DLCO and DTPA/HMPAO in EMPH patients. **Conclusion:** Our results suggest that: (1) at least two different mechanisms in the lungs were at work; (2) the AI damage in EMPH developed mainly in the lipophilic part of the alveoli; and (3) the AI damage presented as slopes of DTPA/HMPAO in our study was different from the traditional pulmonary function such as DLCO.

Key Words: alveolar integrity; pulmonary emphysema; radioaerosol inhalation lung scintigraphy

J Nucl Med 1995; 36:68–72

The lung parenchyma is essentially a three-compartment structure consisting of the alveolar space, the vascular space and the interstitium. The integrity of these compartments, fundamental to the maintenance of normal gas exchange, is preserved by the components of the alveolar capillary membrane. In addition to oxygen, carbon dioxide and water, small solutes and macromolecules move in either direction via both cellular and paracellular routes across the alveolar capillary membrane. Therefore, the integrity of alveoli plays a crucial role in the transfer of fluid and solutes (*1*).

Emphysema is defined in pathological terms as the enlargement or destruction of the alveolar unit (*2*). This term refers to the condition in patients who cough and also have various degrees of dyspnea on exertion. The destruction of the alveolar surface leads to loss of the capillary bed of the alveoli (*3*). In addition, these patients also demonstrate abnormalities at the air/blood interface as judged by carbon monoxide uptake tests (diffusion tests) and hyperinflation, judged clinically by physical examination and x-ray (*4*). Diagnostic procedures for pulmonary emphysema include clinical history, physical examination, radiography, CT and pulmonary function test (*5*). Standard radiology of the chest provides a morphological approach, but is only indicative of emphysema in advanced cases (*5*). Recent reports indicate that there is good correlation between the CT findings and pathologic findings of emphysema (*6,7*). However, interpretation of CT density distributions are time consuming. The pulmonary function test cannot differentiate between anatomical emphysema and other causes of air flow obstruction (*8*). It has been shown that pulmonary ^{99m}Tc-labeled diethylenetriamine pentaacetate (DTPA) or hexamethylpropylene amine oxime (HMPAO) clearance can be used to assess lung injury in various lung diseases (*9–14*). Therefore, ^{99m}Tc-HMPAO and ^{99m}Tc-DTPA radioaerosol inhalation lung imagings should serve as additional or alternative diagnostic modalities for pulmonary emphysema in this study.

MATERIALS AND METHODS

Alveolar integrity (AI) in 17 male patients (age: 65–76 yr who smoked for over 40 yr but stopped for at least 1 yr) with pulmonary emphysema (EMPH) diagnosed by chest x-ray was measured by ^{99m}Tc-DTPA and ^{99m}Tc-HMPAO radioaerosol inhalation lung scintigraphy using a commercial lung aerosol delivery unit. The AI of EMPH patients were compared with the AI of 16 normal controls (age: 63–76 yr, nonsmokers with normal chest

Received Jan. 31, 1994; revision accepted July 21, 1994.

For correspondence and reprints contact: Chia-Hung Kao, MD, Dept. of Nuclear Medicine, Taichung Veterans General Hospital, 160 Taichung Harbor Rd., Section 3, Taichung 40705, Taiwan, Republic of China.

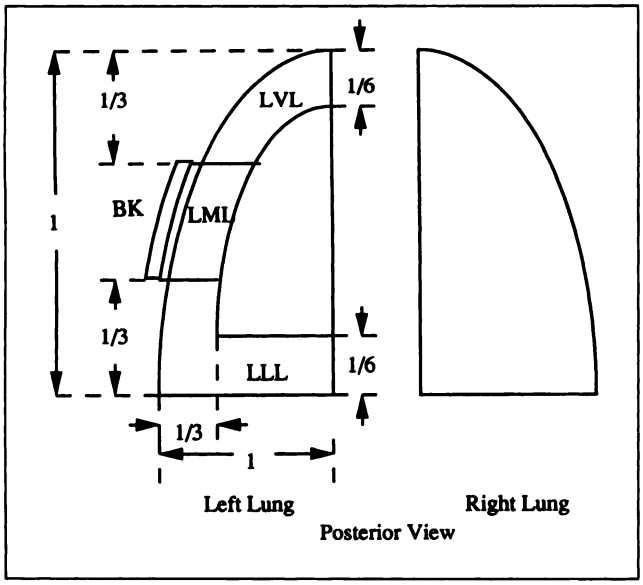

FIGURE 1. How to choose the ROIs in the peripheral regions of the left lung and the selected area of the background (BK) correction. The BK correction formula was: the corrected mean counts/pixel in the ROIs = the original mean counts/pixel in the ROIs − the mean count/pixel in the BK area.

x-rays and pulmonary function tests). The patients were divided into two groups: (A) nine EMPH with normal CO diffusion capacity (DLCO ≧ 80% predicted value) and (B) eight EMPH with abnormal DLCO (<80% predicted value).

The ^{99m}Tc-DTPA/HMPAO radioaerosol clearance speed which was presented as slope (%/min) and which was based on a 30-min imaging acquisition period from lungs to blood was measured in all individuals. A 2-day interval elapsed between the DTPA and HMPAO studies in each individual. The radioaerosols (particle size, approximate aerodynamic median mass diameter was smaller than 1 μm at 7 liters/min air flow rate) were generated from a commercial lung aerosol delivery unit (Aero/Vent, Medi Nuclear) containing 20 mCi of ^{99m}Tc-DTPA/HMPAO in 2 ml of saline. Subjects were in the supine position and inhaled for 2 min from the aerosol delivery unit until the total radioactivity was over 200,000 counts by normal tidal breathing. Data were collected over another 30 min by means of a large-field computerized gamma camera over the posterior view which included the whole chest. During the whole imaging period, the patients were not allowed to swallow the saliva. The data were acquired as a series of 30 consecutive frames, each of 1-min duration and a 64 × 64 matrix with word mode.

After data acquisition, the first image in the series was displayed and three regions of interest (ROIs) were automatically created with the peripheral one-third of the left lung field producing equal subdivisions of the lung into upper, middle and lower third (Fig. 1). The reason for the preference of the left to right lungs for analysis of radioactivity clearance is to avoid the possibly higher background radioactivity from the liver uptake of lipophilic ^{99m}Tc-HMPAO just below the right lung. The reason for the selection of only peripheral portions of the left lung is to exclude the contribution of centrally deposited radioactivity to the clearance values. Radioactivity was corrected for radionuclide decay and background corrected time-activity curves (Fig. 1) were generated individually for each third portion of the peripheral left lung. A power exponential fitting routine was then used to calculate the slopes of the curves. In addition, the total slope of both lungs was calculated to analyze the correlation with DLCO.

TABLE 1
Detailed Patient Data

Patient no.	Age (yr)	Total both lung slopes (%/min) DTPA	HMPAO	DLCO (% predicted value)
1	66	0.50	0.48	178
2	72	0.65	0.21	138
3	66	1.24	0.30	126
4	68	1.17	0.19	122
5	75	1.07	0.15	104
6	70	1.23	0.68	101
7	74	1.53	0.21	86
8	70	0.31	0.25	86
9	71	0.49	0.48	80
10	66	1.82	0.44	79
11	72	0.70	0.40	79
12	74	0.75	0.26	74
13	65	1.65	0.27	70
14	72	0.58	0.30	70
15	69	1.02	0.25	69
16	76	1.01	0.28	54
17	73	0.89	0.25	51

RESULTS

Patient data including age, slopes and DLCO are tabulated in Table 1. The correlation between the value of DLCO and the slopes of DTPA/HMPAO in EMPH patients was not good (Figs. 2 and 3). The scintigraphic results of the study groups are shown in Tables 2 and 3. The clearance (slope) of DTPA aerosols was faster (larger) than that of HMPAO aerosols in each portion of the left lung for any study group ($p < 0.001$, paired t-test). There were significant statistical differences between the normal controls and EMPH patients in the HMPAO study results

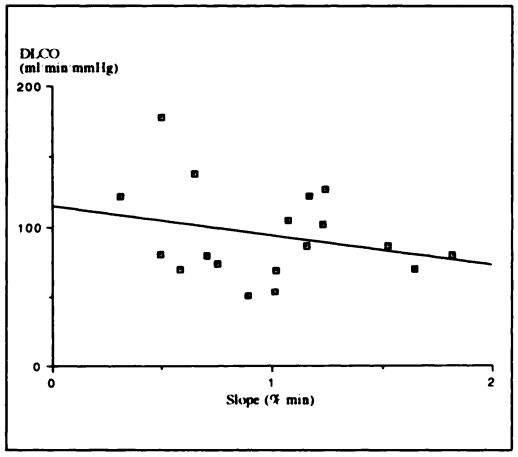

FIGURE 2. Simple regression analysis between the DLCO and the slopes of DTPA was performed using cubic models. The coefficient from the regression equation was Y = 40.56 * X + 80.33, r = 0.166.

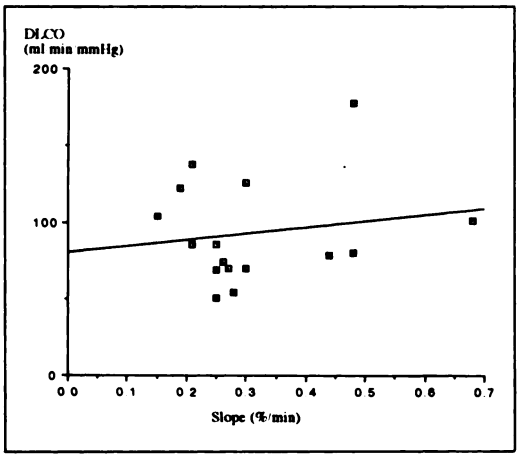

FIGURE 3. Simple regression analysis between the DLCO and the HMPAO slopes performed using cubic models. The coefficient from the regression equation was Y = −21.68 * X + 115.23, r = 0.278.

(Table 4, $p < 0.05$, Mann-Whitney U-test) but not in the DTPA study (Table 4, $p > 0.05$, Mann-Whitney U-test).

DISCUSSION

With emphysema, there is usually slow progressive dyspnea with little or no cough. In moderate to advanced diseases, the diaphragm moves poorly and the accessory muscles of respiration are used. The lungs are resonant over a large area, the breath sounds are usually diminished and faint expiratory rhonchi may be heard. Cardiac and hepatic dullness are diminished. Chest x-rays are helpful in suggesting the diagnosis in moderate to severe emphysema with low flat hemidiaphragms, and enlarged retrosternal clear space, considerable variability in the pulmonary vasculature and often bullous changes (*15*). As emphysema progresses, the more usual tests of pulmonary function become abnormal. Carbon monoxide diffusing capacity is a sensitive test for detection of pulmonary dysfunction, but it lacks diagnostic specificity. The test measures the rate of transfer of CO across the alveolar-capillary membrane (ml CO/min/mmHg). Impaired matching of ventilation and perfusion, alterations in the alveolar-capillary membrane itself, and/or decreases in pulmonary capillary blood volume cause an abnormal reduction of DLCO (*16*). The DLCO is frequently abnormal in chest diseases when other clinical tests, e.g., chest roentgenograms, do not reveal abnormalities (*17*). Common diseases such as emphysema also lower DLCO (*18*).

Radionuclide imaging can readily be used to demonstrate segmental or subsegmental zones of poor ventilation in patients with EMPH. The imaging agent may be ^{81m}Kr, ^{127}Xe or ^{133}Xe gas or, alternatively, a radiolabeled aerosol (*15,19*), which are now used routinely at many centers for detecting lung ventilation based on an initial equilibrium imaging frame. However, serially dynamic lung scintigra-

TABLE 2
Data from ^{99m}Tc-DTPA Radioaerosol Scintigraphic Lung Inhalation

Study groups	Scintigraphy location	Slope (mean ± s.d.)
Normal controls	LUL	1.08 ± 0.72 (%/min)
	LML	1.05 ± 0.74 (%/min)
	LLL	0.88 ± 0.55 (%/min)
	BTL	1.11 ± 0.48 (%/min)
Patient with emphysema	LUL	1.09 ± 0.63 (%/min)
	LML	0.93 ± 0.63 (%/min)
	LLL	1.05 ± 0.47 (%/min)
	BTL	0.98 ± 0.42 (%/min)
Group A DLCO ≧80 (ml/min/mmHg)	LUL	1.19 ± 0.67 (%/min)
	LML	1.15 ± 0.68 (%/min)
	LLL	1.10 ± 0.53 (%/min)
	BTL	0.91 ± 0.40 (%/min)
Group B DLCO <80 (ml/min/mmHg)	LUL	0.98 ± 0.56 (%/min)
	LML	0.70 ± 0.48 (%/min)
	LLL	1.01 ± 0.40 (%/min)
	BTL	1.05 ± 0.42 (%/min)

DLCO = diffusion capacity of CO; LUL = left upper lung; LML = left middle lung; LLL = left lower lung; and BTL = both total lungs.

TABLE 3
Technetium-99m-HMPAO Radioaerosol Scintigraphic Lung Inhalation Results

Study groups	Scintigraphy location	Slope (mean ± s.d.)
Normal controls	LUL	0.12 ± 0.22 (%/min)
	LML	0.27 ± 0.39 (%/min)
	LLL	0.22 ± 0.18 (%/min)
	BTL	0.21 ± 0.14 (%/min)
Patient with emphysema	LUL	0.27 ± 0.14 (%/min)
	LML	0.36 ± 0.19 (%/min)
	LLL	0.39 ± 0.35 (%/min)
	BTL	0.32 ± 0.13 (%/min)
Group A DLCO ≧80 (ml/min/mmHg)	LUL	0.29 ± 0.12 (%/min)
	LML	0.40 ± 0.24 (%/min)
	LLL	0.50 ± 0.41 (%/min)
	BTL	0.33 ± 0.17 (%/min)
Group B DLCO <80 (ml/min/mmHg)	LUL	0.25 ± 0.16 (%/min)
	LML	0.32 ± 0.09 (%/min)
	LLL	0.25 ± 0.16 (%/min)
	BTL	0.31 ± 0.07 (%/min)

TABLE 4
Statistical Analysis Between Normal Controls and Emphysema Patients in the Different Inhalation Scintigraphies

Scintigraphy		Location LUL	LML	LLL
DTPA	Z =	−0.450	−0.360	−0.703
	P	>0.05	>0.05	>0.05
HMPAO	Z =	−2.710	−2.239	−1.405
	P	<0.05*	<0.05*	>0.05

*Significant statistical differences.

phy to calculate alveolar clearance rates of inhaled radioaerosols such as ^{99m}Tc-DTPA or ^{99m}Tc-HMPAO in our study, which represents the alveolar integrity of the patients with EMPH, has not been reported.

Technetium-99m-DTPA gets deposited in the lining layer of the pulmonary epithelial surface and then passes through the epithelial barrier, and once cleared from the lungs, redistributes in the extracellular space of the chest, which includes the interstitial and intravascular spaces of the chest wall and lungs (*20*). Technetium-99m-DTPA aerosol inhalation lung scan is a sensitive marker of the changes of the permeability characteristics of the lung parenchyma. It has been used to investigate epithelial permeability in different physiological conditions (*21,22*), in smokers (*23*) and in various pulmonary disorders (*11,24*). Clearance of ^{99m}Tc-DTPA is increased in patients with diseases known to involve the alveolar-capillary membrane, whether they are cases of adult respiratory distress syndrome (*25*) or interstitial lung disease (*11,26*). In contrast, previous studies have described normal ^{99m}Tc-DTPA clearance in nonsmokers with airflow obstruction, whether in stable asthma (*27,28*) or chronic airflow limitation (*29*).

Technetium-99m-HMPAO is a lipophilic brain imaging agent used for the diagnosis of stroke and dementia. There is pulmonary localization only in the lungs of smokers (*12,13*) and in almost all EMPH patients with a past history of smoking; however, factors of varying degrees of lung uptake are still unknown. Its site of localization is presumably in the pulmonary vascular endothelium. Postulated mechanisms for increased ^{99m}Tc-HMPAO uptake in the smoker's pulmonary vascular endothelial cells include the following: smoking-induced neutrophil stasis in the lung leading to changes of pulmonary endothelial cell function; and smoking-associated mediators such as carbon monoxide, nicotine, nitrogen oxide, tar and formalin, allowing localization of ^{99m}Tc-HMPAO aerosols (*12,13,30*). Therefore, we think that inhaled aerosols of a lipophilic substance, such as ^{99m}Tc-HMPAO, may cross transcellularly using the whole alveolar surface. The clearance of aerosols depends on regional perfusion while hydrophilic aerosols, such as ^{99m}Tc-DTPA, pass by an intercellular pathway and the clearance is diffusion limited (*31*). We find that:

1. Lipophilic HMPAO (transferring cell membranes) was slower than hydrophilic DTPA (transferring intracellular pores) in clearing aerosols deposited in the lungs for all patients, which suggests that at least two different mechanisms were at work in clearing aerosols deposited in the lungs. The results challenge the previous reports which have demonstrated a faster or equal clearance rate for HMPAO than for DTPA (*9,31*).
2. The normal clearance of ^{99m}Tc-DTPA aerosols may result from the preserve of the tight intercellular junctions and that increased clearance of ^{99m}Tc-HMPAO aerosols may be due to the loss of alveolar cell integrity for EMPH in our study. The HMPAO slopes in EMPH patients were larger than in normal controls, which means that AI damage in EMPH develops mainly in the lipophilic part of the alveoli.
3. No good correlation between the DLCO values and slopes of DTPA/HMPAO was found, which suggests that the AI damage presenting as slopes of DTPA/HMPAO in our study was different from the traditional pulmonary function tests such as DLCO.

In conclusion, the serial measurement of alveolar integrity relying on HMPAO inhalation lung scans may have a role to play in monitoring the repair process following injury as in EMPH.

REFERENCES

1. Dolovich MB, Jordana M, Newhouse MT. Methodologic considerations in mucociliary clearance and lung epithelial absorption measurements. *Eur J Nucl Med* 1987;13:S45–S52.
2. West JB. *Pulmonary pathophysiology—the essentials*. Baltimore: Williams & Wilkins; 1977:59.
3. Thurlbeck WM. Morphology of emphysema and emphysema-like conditions. In: *Chronic airflow obstruction in lung disease*. Philadelphia: W.B. Saunders; 1976.
4. Petty TL. Definitions, clinical assessment, and risk factors. In: Petty TL, ed. *Chronic obstruction pulmonary disease*, 2nd edition. New York: Marcel Dekker, Inc.; 1985:1–30.
5. Thurlbeck WM. Overview of the pathology of pulmonary emphysema in the human. *Clin Lab Med* 1983;4:539–559.
6. Muller NL, Staples CA, Miller RR, Abbout RT. Density mask: an objective method to quantitative emphysema using computed tomography. *Chest* 1988;94:782–787.
7. Gould GA, MacNee W, McLean A, et al. CT measurements of lung density in life can quantitate distal airspace enlargement: an essential defining feature of human emphysema. *Am Rev Respir Dis* 1988;137:380–392.
8. Kinsella M, Muller N, Vedal S, et al. Emphysema in silicosis: a comparison of smokers with nonsmokers using pulmonary function testing and computed tomography. *Am Rev Respir Dis* 1990;141:1497–1500.
9. Yeh SH, Liu RS, Wu LC, Peng NJ, Lu JY. Technetium-99m-HMPAO and ^{99m}Tc-DTPA radioaerosol clearance measurements in idiopathic pulmonary fibrosis (IPF) [Abstract]. *J Nucl Med* 1990;31:772.
10. Niden AH, Mishkin FS, Khurana M. Gallium-67-citrate lung scans in interstitial lung disease. *Chest* 1976;62:266–268.
11. Rinderknecht J, Shapiro L, Krauthammer M, et al. Accelerated clearance of small solutes from the lungs in interstitial lung disease. *Am Rev Respir Dis* 1980;121:105–117.
12. Shih WJ, Gruenwald F, Biersack HJ, et al. Technetium-99m-HMPAO diffuse pulmonary uptake demonstrated in cigarette smokers. *Clin Nucl Med* 1991;16:668–672.
13. Shih WJ, Rehm SR, Grunwald F, et al. Lung uptake of ^{99m}Tc-HMPAO in cigarette smokers expressed by lung/liver activity ratio. *Clin Nucl Med* 1993;18:227–230.
14. Takahashi T, Obara T, Ono M, Kikuchi M, Yanagisawa T. Effect of cigratte smoking on diffuse pulmonary uptake of ^{99m}Tc-HMPAO. *Kaku Igaku* 1993; 30:1231–1234.
15. Secker-Walker RH. Obstructive pulmonary disease. In: Atkins HL, ed. *Pulmonary nuclear medicine techniques in diagnosis of lung disease*. New York: Marcel Dekker, Inc.; 1984:109–166.
16. Forster RE, Ogilvie C. The single-breath carbon monoxide transfer 25 years on: a reappraisal. *Thorax* 1983;38:1–9.
17. Epler GR, McCloud TC, Gaensler EA, Minus JP, Carrington CG. Normal chest roentgenograms in chronic diffuse interstitial lung disease. *N Engl J Med* 1978;298:934–939.
18. Gelb AF, Gold WM, Wright RR, Bruch HR, Nadel JA. Physiologic diagnosis of subclinical emphysema. *Am Rev Respir Dis* 1973;107:50–63.
19. Clarke SW, Agnew JE. Current status of nuclear medicine in chronic airflow limitation. *Eur J Nucl Med* 1987;13:S20–S23.
20. Parker JC, Falgout HJ, Parker RE, Granger N, Taylor AE. The effect of fluid volume loading on exclusion of interstitial albumin and lymph flow in the dog lung. *Circ Res* 1979;45:440–450.
21. Meignan M, Rosso J, Leveau J, et al. Exercise increases the lung clearance of inhaled technetium-99m-DTPA. *J Nucl Med* 1986;27:274–280.

22. Meignan M, Rosso J, Robert R. Lung epithelial permeability to aerosolized solutes: relation to position. *J Appl Physiol* 1987;62:902–911.
23. Mason GR, Ulzer JM, Effros RM, Reid E. Rapid reversible alteration of pulmonary epithelium permeability induced by smoking. *Chest* 1983;83:6–11.
24. Rosso J, Guillon JM, Parrot A, et al. Technetium-99m-DTPA aerosol and gallium-67 scanning in pulmonary complications of human immunodeficiency virus infection. *J Nucl Med* 1992;33:81–87.
25. Jones JG, Royston D, Minty BD. Changes in alveolar-capillary barrier function in animals and humans. *Am Rev Respir Dis* 1983;127:51–59.
26. Pantin CFA, Britten A, Lawrence R, Sweatman MCM, Turner-Warwick M. Lung permeability in patients with interstitial lung disease [Abstract]. *Thorax* 1984;39:709.
27. O'Byrne PM, Dolovitch M, Dirks R, Roberts RS, Newhouse MT. Lung epithelial permeability: relation to non-specific airway responsiveness. *J Appl Physiol* 1984;57:77–84.
28. Elwood RK, Kennedy S, Belzberg A, Hogg JC, Pare PD. Respiratory mucosal permeability in asthma. *Am Rev Respir Dis* 1983;128:523–527.
29. Huchon GJ, Russell JA, Barritault LG, Lipavsky AJA, Murray JF. Chronic airflow limitation does not increase respiratory epithelial permeability assessed by aerosolised solute, but smoking does. *Am Rev Respir Dis* 1984; 130:457–460.
30. Riley DJ, Kerr JS. Oxidant injury of the extracellular matrix: potential role in the pathogenesis of pulmonary emphysema. *Lung* 1985;163:1–13.
31. Kawakami K, Tominaga S, Takagi H, et al. Pulmonary clearance of ^{99m}Tc-HMPAO aerosol. *Kaku Igaku* 1990;27:451–457.