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ORIGINAL ARTICLE

Influence of hilar deposition in the evaluation of the alveolar epithelial permeability on ^{99m}Tc-DTPA aerosol inhaled scintigraphy

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Abstract
Purpose. We investigated whether hilar radioaerosol deposition affects the clearance rate of technetium-99m-labeled diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) from peripheral alveolar regions.
Materials and methods. A total of 38 patients underwent ^{99m}Tc-DTPA inhalation lung scintigraphy. Six region of interest (ROI) patterns were adopted: ROI 1 was outlined around the entire hemithorax, and ROIs 2–6 were outlined around the hemithorax but excluded square ROIs of different size in the hilar region. Half-times ($T_{½}$) were calculated with time–activity curves using one-compartment and two-compartment analyses. The $T_{½}$ of ROIs 1–5 were plotted against the $T_{½}$ of ROI 6, and regression lines were obtained with the least-squares method. The absolute values of the differences between surveyed values and regression line were calculated. The Wilcoxon test for trend and a single linear regression model were used to determine statistical significance.
Results. There were significant reductions in the absolute values of the differences between surveyed values and regression line from ROIs 1–5 by one-component analysis and the fast component of two-compartment analysis ($P < 0.001$).
Conclusion. Our results suggest that the deposition of radioaerosol in the hilar region affects the clearance rate of ^{99m}Tc-DTPA from the alveoli in damaged lungs. The hilar region should be excluded from ROIs when alveolar epithelial permeability is evaluated.

Key words ^{99m}Tc-DTPA · Lung clearance · Alveolar epithelial permeability · One-compartment analysis · Two-compartment analysis

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Introduction

Technetium-99m-labeled diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) aerosol inhaled scintigraphy is a rapid, easy to perform, extremely sensitive method for detecting pulmonary epithelial abnormalities.[1] When inhaled, ^{99m}Tc-DTPA particles arrive at the alveolar epithelial surface and then diffuse from airspace into the vascular space. The clearance rate of ^{99m}Tc-DTPA from the lung serves as an index of pulmonary epithelial permeability. Thus, ^{99m}Tc-DTPA aerosol-inhaled scintigraphy has been used in numerous experiments and clinical investigations to assess the integrity of the respiratory epithelium.

However, there is still no consensus regarding which scintigraphic methods and protocols should be used for analyzing pulmonary clearance of ^{99m}Tc-DTPA. Factors known to affect the clearance rate of ^{99m}Tc-DTPA include the type and purity of the radiopharmaceutical prepara-

tion, aerosol particle size, particle deposition site, particle concentration, body position, scanning time, the lung volume during aerosol inhalation and scanning, and the computation method.[2] Differences in the size of inhaled particles and in breathing patterns can affect the site of DTPA deposition. About 60%–80% of particles 1–10 μm in diameter are deposited in the bronchioles, and 40%–60% of particles 1–5 μm in diameter are deposited in the alveoli.[3] Rapid, shallow breathing causes aerosols to be deposited preferentially in the bronchi rather than in the alveoli.[4] The site of aerosol deposition might significantly affect measured solute clearance rates if permeability differs between bronchial and alveolar epithelia and if significant amounts of solute are deposited at both sites.

Clearance rates can be affected by the site of radioaerosol deposition because permeability differs between the bronchial epithelium and alveolar epithelium. Furthermore, whether ^{99m}Tc-DTPA clearance rates depend on the lung region remains controversial. The marked aerosol deposition in the central airway may cause underestimation of alveolar epithelial permeability. Krasnow et al. have suggested that regions of interest (ROIs) in central and peripheral regions should be created individually if information about both lung aerosol deposition and mucociliary clearance are desired.[5] Oberdorster et al. have also suggested that differences between bronchial and alveolar permeability should be considered when results of ^{99m}Tc-DTPA lung permeability studies are interpreted.[6] On the other hand, Mogulkoc et al. have reported that mucociliary clearance from the central airways does not play a significant role in the measurement of $T_{½}$ (the fast compartment of a two-compartment analysis) and that information from the entire lung should be used for the analysis.[7] The previous studies have shown that the methods used to interpret hilar and peripheral clearance rates are valid, and no standard method has been established.

This study was designed to study the effects of proximal bronchial deposition on peripheral alveolar epithelial clearance of ^{99m}Tc-DTPA aerosol.

Materials and methods

Patients

A total of 38 patients were enrolled in this study (19 males, 19 females; ages 9–83 years, mean 50.8 ± 21.6 years). The diagnoses were idiopathic pulmonary fibrosis in 9 patients, collagen diseases in 18 patients (juvenile rheumatoid arthritis in 6, dermatomyositis in 3, Sjögren syndrome in 3, scleroderma in 2, polymyositis/dermatomyositis in 2, dermatomyositis and Sjögren syndrome in 1, scleroderma and Sjögren syndrome in 1), chronic obstructive pulmonary disease in 3 patients, leukemia with suspected interstitial pneumonia in 2 patients, and leukemia with suspected pneumonia, aplastic anemia with suspected pneumonia, Takayasu aortitis, bronchial atresia, cryptogenic organizing pneumonia, and suspected pneumonia in 1 patient each. In all, 33 patients were nonsmokers, and 5 were smokers. The study was approved by the ethics committee of The Jikei University, and informed consent was obtained from all patients.

Radioaerosol inhalation lung scintigraphy

The ^{99m}Tc was eluted from a ^{99}Mo generator (Ultra-Techne Kow; Fujifilm RI Pharma, Tokyo, Japan) and diluted in saline; 370 MBq of sodium pertechnetate was introduced into a vial containing 2.5 mg of DTPA (Techne DTPA Kit; Fujifilm RI Pharma) to produce ^{99m}Tc-DTPA. The aerosol was delivered through an ultrasonic nebulizer (Nesco UN-701; Alfresa Pharma, Osaka, Japan). Aerosol production is significantly more efficient with the ultrasonic nebulizer than the jet nebulizer.[8] Aerosol particles <2 μm in diameter deposit in the peripheral airways.[9] The average diameter of the aerosol particles was 3.54 μm at room temperature (26°C) and humidity (52%) at our institution.

All subjects inhaled the generated ^{99m}Tc-DTPA aerosols during normal tidal breathing in a sitting position until the total radioactivity was greater than 10 000 counts. Immediately after inhalation, the patients were asked to rinse their mouth, oropharynx, and esophagus; and dynamic thoracic images were obtained from the back. The radioactivity counts were recorded at 20 s/frame for 20 min with a low-energy, general-purpose collimator and a large field-of-view gamma camera (ZLC7500; Siemens, Malvern, IL, USA).

Data analysis

To analyze the pulmonary clearance of ^{99m}Tc-DTPA aerosols, six ROI patterns were adopted (Fig. 1). ROI 1 was outlined around the entire hemithorax and included the central airways of the hilar region; and ROIs 2–6 were outlined around the hemithorax but excluded square ROIs (5×5, 8×8, 11×11, 14×14, and 17×17 pixels, respectively) in the hilar region. The pixel size was 3.52 mm. The ROIs in the right and left lung fields were set individually, and 76 lung fields were analyzed.

Time–activity curves of the ^{99m}Tc-DTPA aerosol in the ROI were generated, and the clearance rate was expressed as the half-time ($T_{½}$) obtained from a

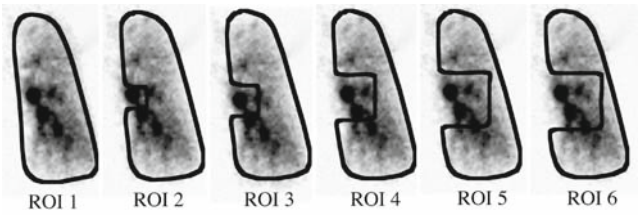

Fig. 1. Regions of interest (ROIs) for analyzing ^{99m}Tc-DTPA aerosol clearance. *ROI 1*, entire hemithorax; *ROI 2*, excluding 5 × 5 pixel ROI in the hilar region; *ROI 3*, excluding 8 × 8 pixel ROI in the hilar region; *ROI 4*, excluding 11 × 11 pixel ROI in the hilar region; *ROI 5*, excluding 14 × 14 pixel ROI in the hilar region; *ROI 6*, excluding 17 × 17 pixel ROI in the hilar region

monoexponential fit (a one-compartment analysis) and a biexponential fit (a two-compartment analysis) on the curves. The results of a two-compartment analysis are expressed as $T_{½}$ for the fast and slow clearance components generated with computer software (Sigmaplot version 7.0; Systat Software, San Jose, CA, USA). No correction was made for background activity in the chest wall or pulmonary circulation because clearance was calculated from data collected shortly after aerosol inhalation.[10]

The $T_{½}$ of ROIs 1–5 were plotted against the $T_{½}$ of ROI 6, and the regression line was obtained with the least-squares method. The absolute values of the differences between surveyed values and the regression line were calculated with one-compartment and two-compartment analyses.

Statistical analysis

Statistical analyses were performed using STATA software package (version 9.0; STATA, College Station, TX, USA). The absolute values of the differences are expressed as medians and 25th and 75th percentiles. The Wilcoxon test for trend and the single linear regression model were used to determine statistical significance.[11] $P < 0.001$ was considered to indicate statistical significance.

Results

We evaluated the differences of the $T_{½}$ between obstructive lung disease and nonobstructive lung disease first because the latter was expected to have less deposition pattern in pulmonary hilum. However, there were no significant differences in the $T_{½}$ of ROIs 1–6 in one-compartment analysis, the fast component of a two-compartment analysis, and the slow component of a two-compartment analysis ($P > 0.05$, Mann-Whitney's U-test), except for ROI 5 in the fast component of a two-compartment analysis ($P = 0.02$). Hence, we did not make the division between obstructive lung disease and nonobstructive lung disease.

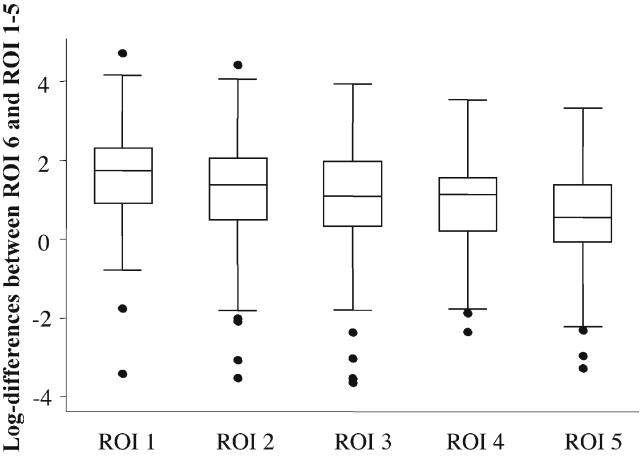

Fig. 2. Box and whisker plot showing the differences between surveyed values and the regression line for each ROI against ROI 6 in a one-compartment analysis in natural logarithms. The box represents the 25th and 75th percentiles; the median is shown by a *horizontal line*. The *whiskers* represent the upper and lower ranges. There was significant reduction of the absolute value in ROIs 1–5 ($P < 0.001$)

Table 1. Correlation coefficient between the $T_{½}$ of ROI 6 and the $T_{½}$ of ROIs 1–5

Analysis	ROI 1	ROI 2	ROI 3	ROI 4	ROI 5
One compartment	0.673	0.746	0.831	0.958	0.958
Two compartment					
Fast	0.488	0.761	0.746	0.863	0.871
Slow	0.482	0.686	0.728	0.741	0.862

$T_{½}$, half-time; ROI, region of interest

There were positive linear correlations between the $T_{½}$ of ROI 6 and the $T_{½}$ of ROIs 1–5 on plots of the $T_{½}$ of ROI 6 versus ROIs 1–5. The correlation coefficients in the one-compartment analysis, fast component of a two-compartment analysis, and slow component of a two-compartment analysis are shown in Table 1. The Wilcoxon test for trend and the single linear regression model were applied to estimate the differences between surveyed values and the regression line. The absolute values of the differences in each ROI are shown in Fig. 2 (one-compartment analysis), Fig. 3 (fast component of a two-compartment analysis), and Fig. 4 (slow component of a two-compartment analysis) in natural logarithms.

There were significant reductions of the absolute value in ROIs 1–5 in a one-compartment analysis and the fast component of a two-compartment analysis ($P < 0.001$). There was no significant reduction of the absolute

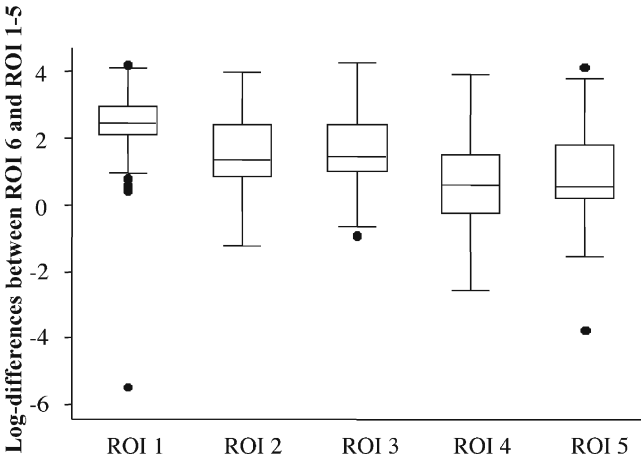

Fig. 3. Box and whisker plot showing the differences between surveyed values and the regression line for each ROI against ROI 6 in the fast component of a two-compartment analysis in natural logarithms. There was significant reduction of the absolute value in ROIs 1–5 ($P < 0.001$)

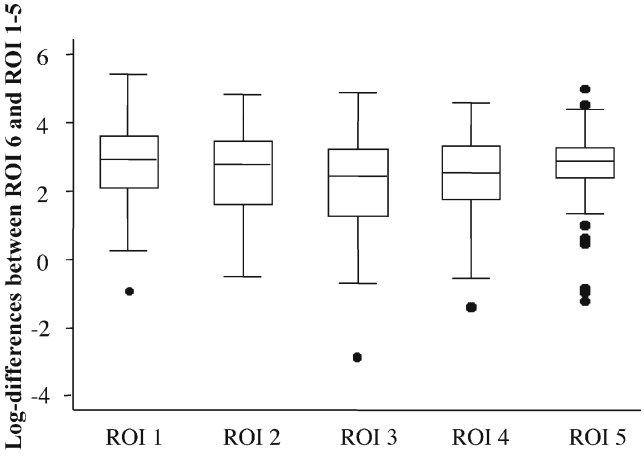

Fig. 4. Box and whisker plot showing the differences between surveyed values and the regression line for each ROI against ROI 6 in the slow component of a two-compartment analysis in natural logarithms. There was no significant reduction of the absolute value in ROIs 1–5

value in ROIs 1–5 in the slow component of a two-compartment analysis.

Discussion

We investigated whether hilar radioaerosol deposition affects DTPA clearance from peripheral alveolar regions. In this study, there was significant reduction of the absolute value of the difference between the surveyed value and the regression line from ROI 1 to ROI 5 in a one-compartment analysis and the fast component of a two-compartment analysis. We believe that the clearance rate differs with changes in the area of the hilar region excluded from the ROI, and this relation suggests that the mechanism of ^{99m}Tc-DTPA clearance differs between the hilar region and peripheral alveolar regions. Several reasons for this difference in clearance rate have been suggested. One possibility is a difference between the alveolar and bronchial epithelia in the physiological mechanism of absorption of ^{99m}Tc-DTPA. Bennett and Ilowite found that the epithelial absorption of ^{99m}Tc-DTPA in vivo is more rapid in alveoli than in the bronchial airways.[12] Oberdorster et al. reached a similar conclusion through experiments in dogs that alveolar absorption of ^{99m}Tc-DTPA is more rapid than bronchial absorption.[6]

A second possible reason for the difference in ^{99m}Tc-DTPA clearance rates between the hilar region and peripheral alveolar regions is that the diffusion distance from the airway surface to the capillaries is much larger in the bronchi than in the alveoli. Effros and Mason suggested that the rate of ^{99m}Tc-DTPA absorption from the epithelial surface correlates with the ratio of the airway surface to the volume of the epithelial lining fluid. This ratio is probably much smaller in the bronchi than in the alveoli because of the smaller surface area covered by a thicker layer of fluid in the bronchi and the larger surface area covered by a thinner layer of fluid in the alveoli.[13]

A third possible reason for the difference in ^{99m}Tc-DTPA clearance rate between the hilar region and peripheral alveolar regions is pulmonary damage caused by various diseases and factors, including adult respiratory distress syndrome (ARDS)[14]; noncardiogenic pulmonary edema[15]; asbestosis[16]; coal worker's pneumoconiosis[17] and other pneumoconioses[18]; human immunodeficiency virus (HIV) infection[19]; interstitial lung diseases, such as sarcoidosis,[18] idiopathic pulmonary fibrosis,[18] hyaline membrane disease,[20] fibrosing alveolitis associated with systemic sclerosis,[21] and cryptogenic fibrosing alveolitis[21]; cigarette smoking[22]; use of crack cocaine[23]; and radiation pneumonitis.[24] Increased pulmonary epithelial permeability increases the rate of ^{99m}Tc-DTPA clearance, and thickening of the alveolar epithelium reduces diffusion and decreases ^{99m}Tc-DTPA clearance.

We investigated the clearance rate of ^{99m}Tc-DTPA by means of a two-compartment analysis in our defined ROIs. Under some conditions in which the alveolar capillary membrane is damaged, the clearance curve has two components. The physical basis of the two compartments is unclear, but the fast component has been suggested to represent clearance from damaged alveoli with increased permeability, whereas the slow component represents clearance from essentially normal

lung.[14,25] Biexponential clearance is always abnormal and indicates greater lung injury than monoexponential clearance. Biexponential ^{99m}Tc-DTPA clearance has been found in several groups, including patients with edema from ARDS,[14] HIV infection,[19] or hyaline membrane disease,[20] and patients without edema after exposure to coal dust[17] or crack cocaine.[23] In the present study, we found that the absolute value of the difference between surveyed values and the regression line from ROIs 1–5 had a significant reduction in the fast component of a two-compartment analysis. We believe ^{99m}Tc-DTPA deposition in the hilar region affects the clearance rate from the peripheral region of the damaged lung in both the one-compartment analysis and the fast component of a two-compartment analysis.

The biexponential clearance also reflects the presence of bronchial and alveolar transport mechanisms.[26] The reason there was no significant reduction of the absolute value in the slow component of a two-compartment analysis is that the slow component indicates the bronchial transport mechanism after fast DTPA clearance of smaller particles from the damaged alveoli (fast component).

Conclusion

We calculated the clearance rate of ^{99m}Tc-DTPA using a one-compartment and two-compartment analyses in each ROI. We conclude that ROIs that include the hilar region affect the clearance rate from the alveolar region in the injured lung; and we therefore suggest that ROIs should exclude the hilar region when lung epithelial permeability is being estimated.

References

1. O'Doherty MJ, Peters AM. Pulmonary technetium-99m diethylene triamine penta-acetic acid aerosol clearance as an index of lung injury. Eur J Nucl Med 1997;24:81–7.
2. Smith RJ, Hyde RW, Waldman DL, Freund GG, Weber DA, Utell MJ, et al. Effect of pattern of aerosol inhalation on clearance of technetium-99m-labeled diethylenetriamine pentaacetic acid from the lungs of normal humans. Am Rev Respir Dis 1992;145:1109–16.
3. Salvaggio JE. Inhaled particles and respiratory disease. J Allergy Clin Immunol 1994;94:304–9.
4. Agnew JE, Pavia D, Clarke SW. Mucus clearance from peripheral and central airways of asymptomatic cigarette smokers. Bull Eur Physiopathol Respir 1986;22:263–7.
5. Krasnow A, Isitman A, Collier D, Effros R, Hellman R, Palmer D, et al. Diagnostic applications of radioaerosols in nuclear medicine. In: Freeman L, editors. New York: Raven; 1993. p. 123–93.
6. Oberdorster G, Utell MJ, Morrow PE, Hyde RW, Weber DA. Bronchial and alveolar absorption of inhaled ^{99m}Tc-DTPA. Am Rev Respir Dis 1986;134:944–50.
7. Mogulkoc N, Brutsche MH, Bishop PW, Murby B, Greaves MS, Horrocks AW, et al. Pulmonary (99m)Tc-DTPA aerosol clearance and survival in usual interstitial pneumonia (UIP). Thorax 2001;56:916–23.
8. Waldman DL, Weber DA, Oberdorster G, Grago SR, Utell MJ, Hyde RW, et al. Chemical breakdown of technetium-99m DTPA during nebulization. J Nucl Med 1987;28:378–82.
9. Dolovich PEng MA. Influence of inspiratory flow rate, particle size, and airway caliber on aerosolized drug delivery to the lung. Respir Care 2000;45:597–608.
10. Coates G, O'Brodovich H. Extrapulmonary radioactivity in lung permeability measurements. J Nucl Med 1987;29:903–6.
11. Cuzick J. A Wilcoxon-type test for trend. Stat Med 1985;4: 87–90.
12. Bennett WD, Ilowite JS. Dual pathway clearance of ^{99m}Tc-DTPA from the bronchial mucosa. Am Rev Respir Dis 1989; 139:1132–8.
13. Effros RM, Mason GR. Measurements of pulmonary epithelial permeability in vivo. Am Rev Respir Dis 1983;127: S59–65.
14. Jones JG, Minty BD, Royston D. The physiology of leaky lungs. Br J Anaesth 1982;54:705–21.
15. Mason GR, Effros RM, Uszler JM, Mena I. Small solute clearance from the lungs of patients with cardiogenic and noncardiogenic pulmonary edema. Chest 1985;88:327–34.
16. Gellert A, Winter R, Uthayakumar S. Bronchoalveolar lavage and clearance of ^{99m}Tc-DTPA in asbestosis. 1984;39:709.
17. Susskind H, Rom WN. Lung inflammation in coal miners assessed by uptake of ^{67}Ga-citrate and clearance of inhaled ^{99m}Tc-labeled diethylenetriamine pentaacetate aerosol. Am Rev Respir Dis 1992;146:47–52.
18. Rinderknecht J, Shapiro L, Krauthammer M, Taplin G, Wasserman K, Uszler JM, et al. Accelerated clearance of small solutes from the lungs in interstitial lung disease. Am Rev Respir Dis 1980;121:105–17.
19. Rosso J, Guillon JM, Parrot A, Denis M, Akoun G, Mayaud C, et al. Technetium-99m-DTPA aerosol and gallium-67 scanning in pulmonary complications of human immunodeficiency virus infection. J Nucl Med 1992;33:81–7.
20. Jefferies AL, Coates G, O'Brodovich H. Pulmonary epithelial permeability in hyaline-membrane disease. N Engl J Med 1984;311:1075–80.
21. Wells AU, Hansell DM, Harrison NK, Lawrence R, Black CM, du Bois RM. Clearance of inhaled ^{99m}Tc-DTPA predicts the clinical course of fibrosing alveolitis. Eur Respir J 1993;6: 797–802.
22. Jones JG, Minty BD, Lawler P, Hulands G, Crawley JC, Veall N. Increased alveolar epithelial permeability in cigarette smokers. Lancet 1980;1:66–8.
23. Susskind H, Weber DA, Volkow ND, Hitzemann R. Increased lung permeability following long-term use of free-base cocaine (crack). Chest 1991;100:903–9.
24. Susskind H, Weber DA, Lau YH, Park TL, Atkins HL, Franceschi D, et al. Impaired permeability in radiation-induced lung injury detected by technetium-99m-DTPA lung clearance. J Nucl Med 1997;38:966–71.
25. Coates G, O'Brodovich H, Dolovich M. Lung clearance of ^{99m}Tc-DTPA in patients with acute lung injury and pulmonary edema. J Thorac Imaging 1988;3:21–7.
26. Steyn PF, Gillette S, Gillette EL. Biological half-life of aerosolized Tc-99m diethylenetriaminepentaacetate in various lung regions of clinically normal beagles. Am J Vet Res 1994; 55:1371–6.