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Topics in Pulmonary Nuclear Medicine

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INTRODUCTION

REVIEWING THE PUBLICATIONS of past few years on nuclear pulmonology, we notice that many of them are about lung tumors and pulmonary circulation abnormality, followed by COPD and infectious diseases (Fig. 1). Ventilation-perfusion studies are predominant as to methods as shown in Fig. 2. An increase in PET studies has also been noticed over the past few years. Considering the global trend of these publications, this article reviews ventilation-perfusion scintigraphy and the evaluation of mucocilliary movement, lung epithelial permeability and the distribution of therapeutic agents inhaled by means of aerosols.

VENTILATION AND PERFUSION

The most recent topic in ^{133}Xe studies is dynamic SPECT with the three head camera. Figure 3[1] shows a case of emphysema. The delay in the washout of ^{133}Xe gas in the peripheral area is clearly seen. A better resolution of the abnormalities, whether they are central or peripheral, has become possible with SPECT, and it can be useful for the early detection of ventilatory disturbances and the diagnosis of diseases.

Other useful aspects of xenon studies include follow-up of the therapy and deciding on the withdrawal time for the drug. Abnormalities cannot be detected in pulmonary function tests, since the lesion is focal, especially in infectious diseases or chronic bronchitis. Even after the X-ray and CT have shown normal results, focal abnormalities remain in the xenon tests. Consequently, we believe that the treatment should be continued as long as abnormalities remain in the xenon tests, particularly in cases of diffuse panbronchiolitis.

^{81m}Kr gas is also available for use in routine clinical examinations. The characteristics of ^{81m}Kr are indicated in Table 1. It is possible to quantitatively evaluate changes in the ventilatory volume by maintaining a constant ^{81m}Kr-gas concentration during continuous inhalation. It is also possible to obtain various items of physiological information, especially related to respiratory impedance and compliance, by having the subject inhale a small amount of gas as a bolus. Thirdly, this makes various challenge tests possible.

We keep the ^{81m}Kr gas concentration constant by attaching a fan to the mouthpiece during continuous inhalation. By this method, a linear relationship is obtained between the ^{81m}Kr concentration and the ventilatory volume. Figure 4[2] shows regional changes in ventilation after MDI (metered dose inhaler) therapy in a patient with asthma, and there are the sites where ventilation was improved by MDI inhalation therapy, and those where it had deteriorated. These deterioration sites explain the temporary decrease in PaO_2 in blood gas following MDI inhalation.

Next, the results of a bolus inhalation of ^{81m}Kr in an asthmatic patient are shown in Fig. 5 (a).[2] When the bolus gas was inhaled quickly, a defect appeared in the right lung, as shown by the arrow, but when it was slowly inhaled, it disappeared. This is because, as shown in the

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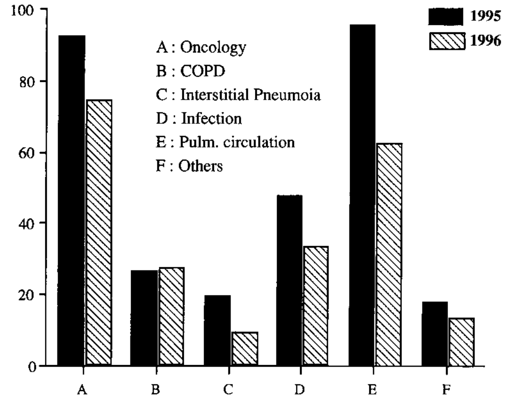


Fig. 1 Publications of pulmonary nuclear medicine.
— Classification by disease —

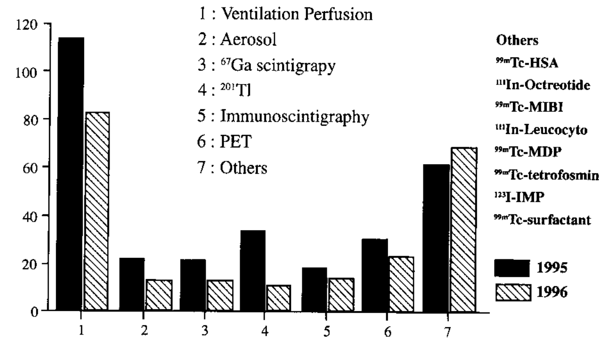


Fig. 2 Publications of pulmonary nuclear medicine.
— Classification by methodology —

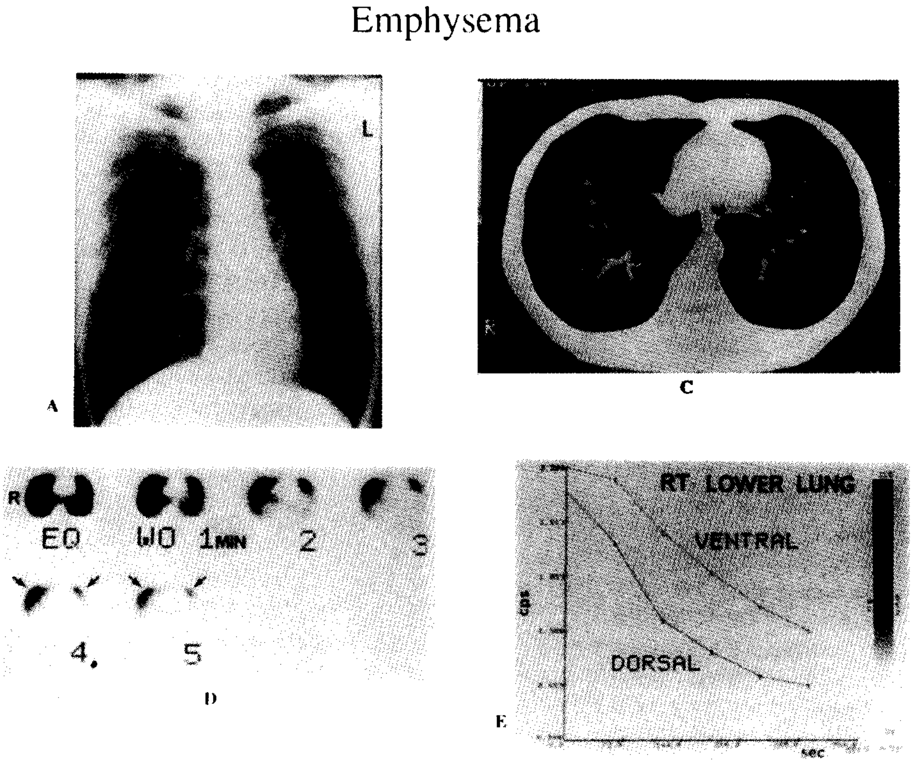


Fig. 3 ^{133}Xe SPECT of emphysema. The washout delay of ^{133}Xe gas in the peripheral area is clearly seen (as shown by arrows in the panel D).

Table 1 The characteristics of ^{81m}Kr

1. Constant concentration		
Continuous inhalation	→	Regional ventilation (Semiquantitative, Dynamic change)
2. Bolus inhalation		
Inhalation speed	→	Respiratory impedance
Inhalation level of lung volume	→	Static compliance
3. Challenge tests		
Exercise		
Pharmacologic		

lower schema, a turbulent flow occurs in the stenosis of the central airway when the inhalation speed has been increased. This occurs due to the impedance changes caused by the turbulent flow, and it occurs in the stenosis of the central airway. Figure 5 (b) shows the inhalation ratio of the $^{13}N_2$ gas detected by PET and the ratio of respiratory impedance in the left and right lungs, when stenosis occurs at 0%, 50% and 70%, found by inflating a balloon catheter inserted into the left main bronchus. And when the gas was inhaled slowly (1 Hz), the left to right (L/R) ratio was 1.0, but when it was inhaled quickly (10 Hz), the L/R ratio for inhaled $^{13}N_2$ gas decreased whereas that of the respiratory impedance increased, as the stenosis becomes noticeable.[3] This experimental study supports

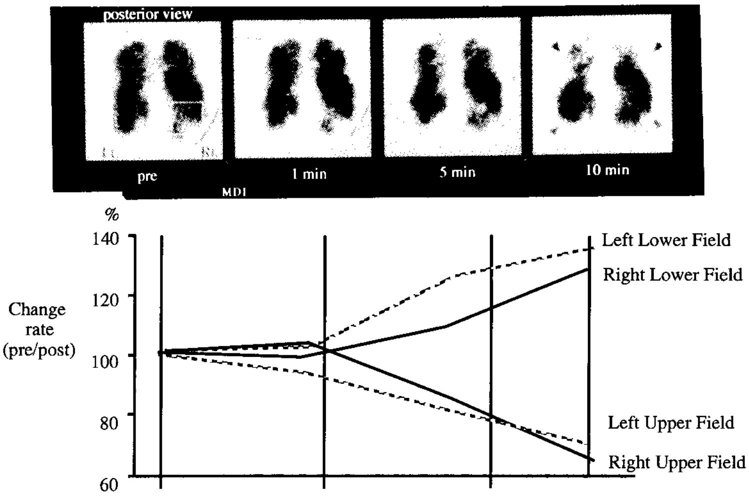


Fig. 4 Regional changes in the ventilation after MDI (metered dose inhaler). Therapy on a patient with asthma. Ventilation in the both upper lung fields is decreased after MDI.

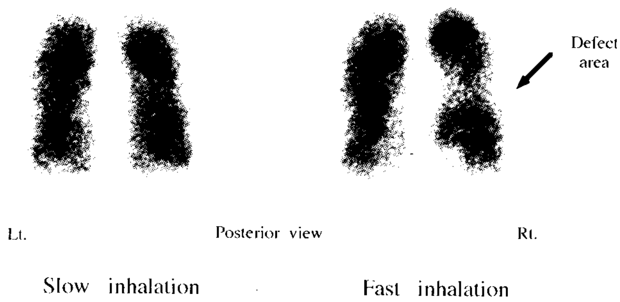


Fig. 5 (a) When the bolus gas was inhaled with a fast speed, a defect appeared in the right lung as shown by the arrow, but when it was slowly inhaled, it disappeared.

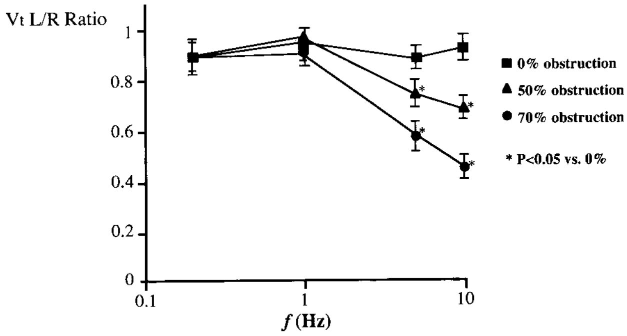


Fig. 5 (b) L/R ratio of tidal volume (VT) as functions of frequency and degree of left main-stem bronchial obstruction.

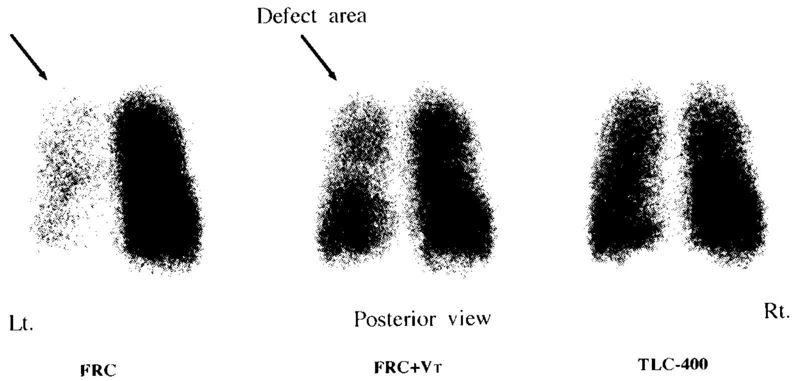


Fig. 6 An asthma patient. When the gas is inhaled from the FRC level, it does not enter the left lung, whereas, when the level of the lung volume is increased to TV and TLC, the gas is inhaled in both sides of the lungs.

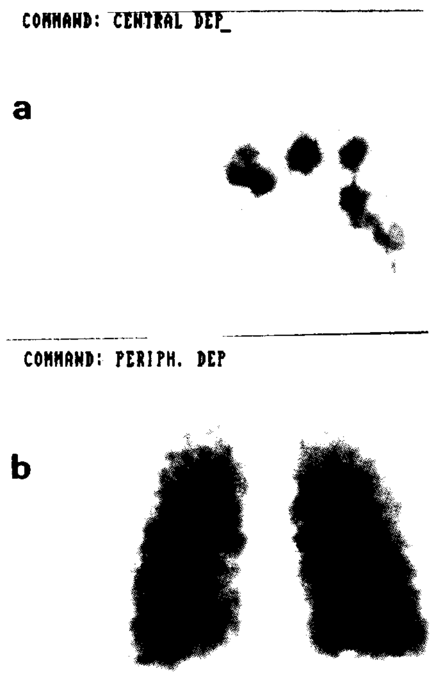


Fig. 7 The distribution of the methacholine labeled with ^{99m}Tc. a. aerosol size 9 μ. b. aerosol size 1 μ.

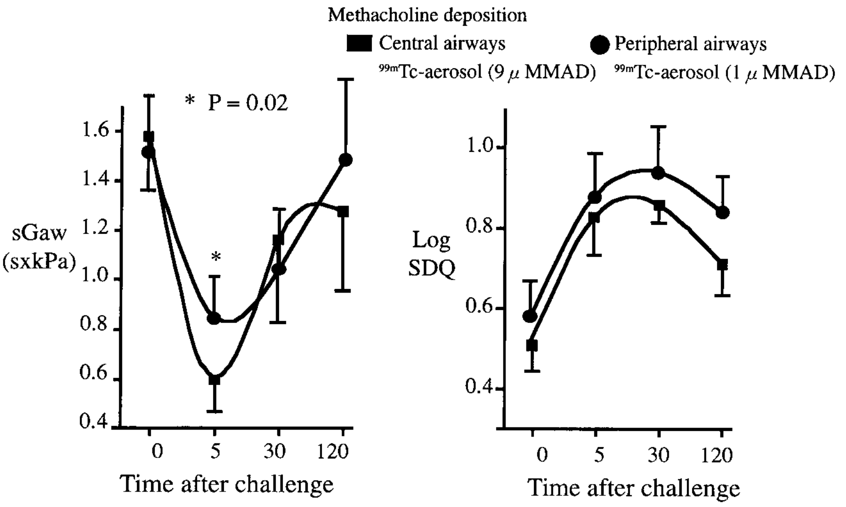


Fig. 8 Action site of inhaled methacholine aerosol.

Table 2 Characteristics of Technegas

Technegas generator
Ultrafine particles of carbon which mimics the intrapulmonary gas distribution
Readily available
Available for ventilation SPECT

our clinical results. In the obstruction of the peripheral airway, the defect gets bigger with slow inhalation.

We next observe the compliance by changing the gas inhalation lung volume. Figure 6[2] indicates an asthma patient. When the gas is inhaled from the functional residual capacity (FRC) level, it does not enter the left lung, but when the lung volume is increased to tidal volume (TV) and total lung capacity (TLC), the gas is inhaled in both sides of the lung. This is due to the decrease in compliance in the left lung. The penetration of the drug in the left lung can be obtained by increasing the lung volume at inhalation, and this is useful in evaluating the distribution of the pharmaceuticals in the inhalation therapy method.

The usefulness of technegas studies is highly enhanced with SPECT imaging. In recent years, pertechnegas with low radiation has been produced by using the technegas generator, and it is used in ventilatory studies. Since this tracer is cleared from the alveolar wall, it is also used to evaluate lung epithelial permeability. Information related to the hemodynamics of the lung, obtained by nuclear medicine, is listed in Table 2. Pulmonary embolism is a most useful indication of perfusion scintigraphy. Several diagnosis criteria (PIOPED, Biello, & Mc Neil) are used. On ROC curve analysis of these three criteria, the accuracy of the criteria of Biello was highest. In addition to these criteria, some other signs that can be useful, such as the peripheral stripe sign, the enhanced V/Q mismatch sign, and the segmental contour pattern, should be considered.

The stripe sign consisted of the presence, on the perfusion images, of a stripe of perfused lung tissue between a perfusion defect and the adjacent pleural surface.[4] The presence of the stripe sign accurately predicted the absence of pulmonary embolism.

The enhanced V/Q mismatch is a regional area of increased ventilation radioactivity in the embolized region of the lung that is more than the normal ventilation radioactivity in the adjacent or contralateral normally perfused lung.[5] The stripe sign contour pattern is a finding of V/Q mismatch, which demonstrates bilateral, patchy, non-segmental defects. This finding is seen in pulmonary veno-occlusive disease, primary pulmonary hypertension and microthromboembolic disease.[6]

The evaluation obtained by combining these findings leads to a decrease in cases belonging to low probability of the PIOPED criteria, and this is useful for the improvement of specificity.

MUCOCILLIARY MEASUREMENT

1) Probe for the Inhalation Therapy

The accurate evaluation of the distribution of the inhaled drugs is a decisive factor for the therapy effect. The distribution of inhaled particles, the particle size, the inhalation speed, the lung volume level for inhalation and the application of a spacer are considered to be other influential factors. Figure 7[7] shows the distribution of the methacholine labeled with ^{99m}Tc, and it shows the different patterns of aerosol distribution in its changed particle size. Aerosol with a particle size of 9 μ is used in the upper figure and most of it is deposited in the central airways. On the other hand, aerosol with a particle size of 1 μ is used in the lower figure, and it is evenly distributed in the lung field.

What effect the deposit pattern of these two cases has on pulmonary function is indicated in Fig. 8. The left side of the figure shows the changes in the conductance (sGaw) as an index of the response in the large airways. The conductance had significantly decreased with the 9 μ aerosol five minutes later, suggesting stenosis in the

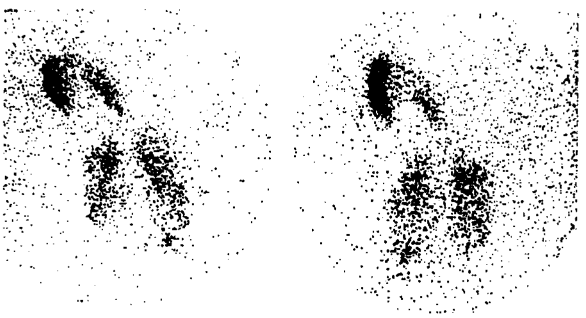


Fig. 9 Image after inhalation of one puff of radiolabeled salbutamol from an MDI by means of a spacer with mask.

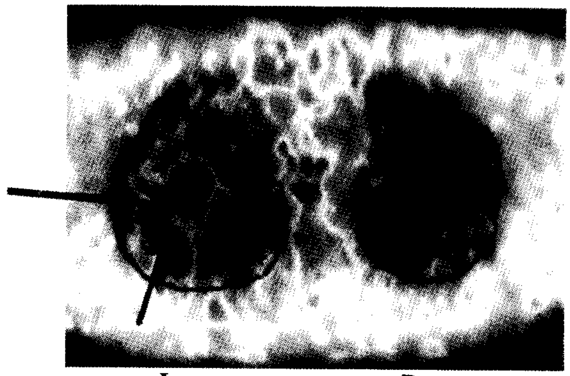


Fig. 10 [18]FDG PET after injecting allergen in the left upper lung field in a case with asthma under bronchoscopy. Injected site is well shown as a hot area (as showed by arrows).

central airways. On the other hand, the right side indicates the unevenness of perfusion (Log SDQ), as an index of changes in the peripheral airways. Both of them had changed in the same way. Perfusion changes occurred slowly, compared to the conductance, because the tracer, which had been deposited in the central airways, was absorbed from the bronchial mucosa and had moved to the capillaries of the peripheral airways. This suggests the necessity of choosing the aerosol size in asthma therapy, according to whether the asthma are of the central airway obstruction type or of the peripheral type.[8]

Various types of spacers are used to avoid the influence of lung volume at inhalation. Figure 9[9] shows the distribution of the inhaled Salbutamol labeled with Tc, and since it has been inhaled by using a spacer, it is evenly distributed within the lung, but the deposition rate within the lung is low, about 2% of the inhaled volume, and more than 90% was left within the spacer. It is therefore necessary to perform deep breathing in this case. This result suggests that the drug should be inhaled from a higher lung volume level in this case.

The distribution of inhaled drug is influenced by the lung volume level from which the drug is inhaled. Inhalation from the FRC level does not result in penetration of the drug in the left lung as shown in Fig. 6, but the gas is evenly inhaled in the (FRC + TV) whole lung, when it is inhaled from the higher level, as shown in the middle and right (TLC) images.

Table 3 Indication of measurement of mucocilliary movement

1. Evaluation of non-respiratory function
Diffuse panbronchitis
Bronchectasis
Asthma
Carcinoma
Primary ciliary dyskinesia syndrome
(immotile-cilia syndrome)
Kartagener's syndrome
2. Effect of pharmacological agents
Mucolytics & expectorants
Bronco dilator
Beta-agonists, Beta antagonists
Corticosteroids
Antibiotics
3. Effect of physical therapy
Postural drainage
Tapping effect
Stent therapy

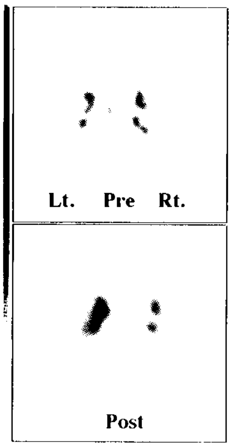
Table 4 Diseases with increased pulmonary epithelial permeability

ARDS (acute respiratory distress syndrome)
Idiopathic interstitial pneumonia
Hypersensitive pneumonitis
Sarcoidosis
Carinii pneumonia
Pulmonary embolism
Asthma
Smoking lung
Inhalation injury

Steroid inhalation therapy has been used in asthma for the treatment of inflammatory processes. Figure 10[10] indicates [18]FDG PET after injecting Allergen in the left upper lung field in a patient' with asthma. [18]FDG, which results in glycolysis in the inflammatory cells, is clearly accumulated in the area of allergic reaction. This suggests the suitability of the steroid therapy.

2) The Mucocilliary Movement

The evaluation of mucocilliary movement, as indicated on Table 3,[11] is used for the evaluation of non-respiratory function, for the effects of pharmacological agents, for physical therapy and so on. The method includes the follow up of MAA droplets deposited under bronchoscopy on the trachea, the cinescintigraphy which evaluates the dynamic trace of the movement of the aerosols which have been deposited in the large bronchi with aerosol inhalation, and the methods for measuring the velocity of the aerosols deposited in the lung fields. Each of these methods has advantages.



Distribution of
^{99m}Tc-HSA aerosole

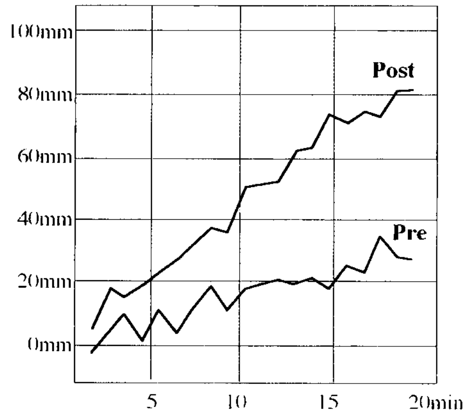


Fig. 11 Effect of Roxithromycin on mucous transport of patient with Cr. B. Asthma. The change in the mucocilliary velocity before and after therapy.

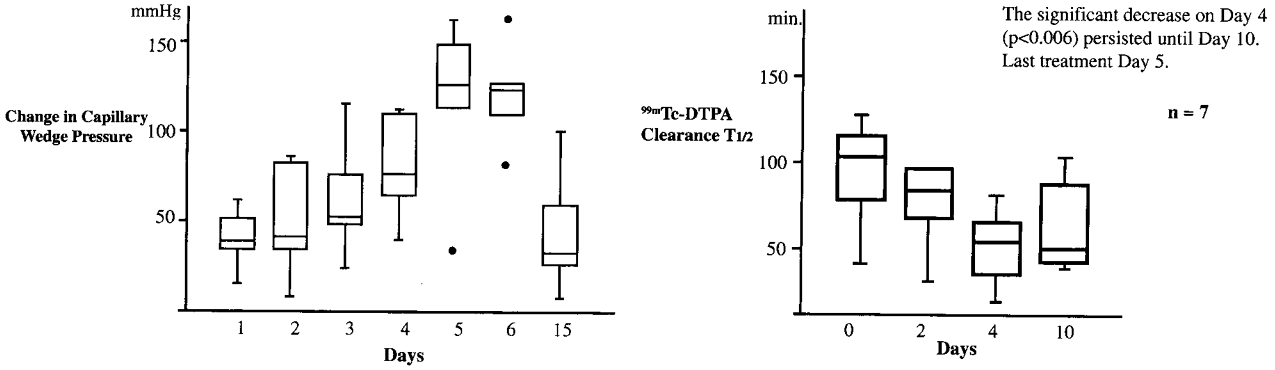


Fig. 12 Left : Changes in capillary wedge pressure during rIL-2 treatment. It decreased after five days. Right: ^{99m}Tc-DTPA clearance during rIL-2 treatment. The significant decrease on day 4 ($p < 0.006$) persisted until day 10. Last treatment day 5.

Figure 11 indicates the changes in the mucocilliary velocity before and after therapy in a patient with asthma. The ordinate shows the distance that covered and the abscissa indicates the time. The mucocilliary velocity is clearly improved after therapy. We have evaluated the regional mucocilliary velocity in diffuse pan-bronchiolitis (DPB). The velocity decreases in the lower lung field in DPB.

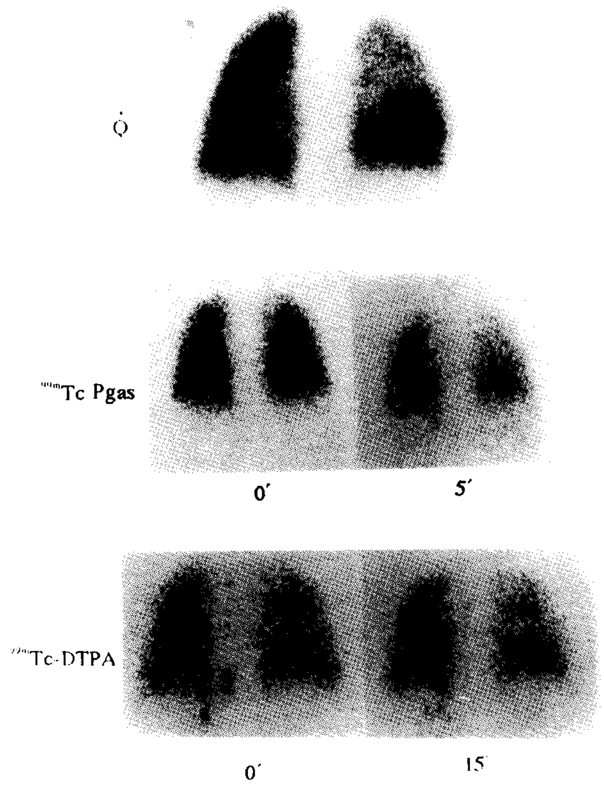
3) Epithelial Permeability

Lung epithelial permeability is the only *in vivo* method used in studying the damage to alveolar-capillary integrity. Measurements of lung epithelial permeability are listed in Table 4. It is accelerated with various pathophysiological conditions. The left side of Fig. 12 shows the changes in capillary wedge pressure in the cases in which IL-2 therapy was performed for metastatic cancer. The wedge pressure increases gradually following the administration of IL-2, and it decreases with the withdrawal of the drug after 5 days of administration.

The right side of the Fig. 12 shows the DTPA clearance. The clearance is accelerated by the IL-2 administration, while it is improved with the cessation of the agent. It is therefore useful to detect the side effects of the drug on alveolar-capillary integrity in an early stage and to evaluate the therapeutic results for various interstitial pulmonary diseases.[12]

Compared with the results of BAL, there is a significant correlation between the lymphocytes and the DTPA clearance, while there is no correlation with the neutrophils, which correlate with ^{67}Ga uptake.

Recently, pertechnegas has also been used instead of DTPA. Figure 13 shows the clearance of DTPA and that of pertechnegas in pulmonary embolism. The clearance of DTPA in the middle column and that of pertechnegas in the lower column are both accelerated in the defect in the right upper lung field which is shown in the lung perfusion scintigraphy of the upper column. The results of our study indicate that the clearance of pertechnegas is accelerated in pulmonary embolism, and a correlation with DTPA is also observed. There are some reports about the application of pertechnegas for the measurement of epithelial permeability in interstitial lung diseases. Because pertechnegas particles are smaller than those of DTPA, it penetrates into the alveoli, even in COPD. The setting of ROI in the lung fields is therefore easily and



Pulmo Embolism

Fig. 13

accurately, done without the effect of hot spots. We think that pertechnegas is a radioactive tracer which should be studied further.

I have reported here on the ventilation-perfusion scintigraphy, the mucocilliary movement, and the evaluation of the lung epithelial permeability, including some recent topics.

CONCLUSION

Recent advances in nuclear pulmonology involve the evaluation of non-respiratory function by radionuclide medicine and tumor imaging in the lungs, but ventilation-perfusion studies are ever more important now that CT and MR are being widely used.

In this article, recent trends in ventilation-perfusion scintigraphy were reviewed, and the clinical importance of the measurement of mucocilliary movement and epithelial permeability have been stressed for the management of chronic obstructive lung diseases.

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