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Evaluation of ^{99m}Tc-HMPAO Scintigraphy for Irradiated Lung in Rabbits : Detection of Pulmonary Microvascular Injury

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家兎放射線照射肺に対する ^{99m}Tc-HMPAO 肺シンチグラフィの検討
—肺血管内皮細胞障害の検出能について—

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^{99m}Tc-HMPAOが，肺血管内皮細胞の障害を反映するトレーサとなり得るかどうかを家兎の放射線照射肺を用いて検討した．

方法は，24家兎の片肺に50 Gy放射線照射し照射後24時間，2日，14日，28日の各々で^{99m}Tc-HMPAO肺シンチグラフィを施行した．データ収集は^{99m}Tc-HMPAO静注直後より1 frame/secで1分間，引き続いて1 frame/minで30分間行い，照射側肺と対側非照射肺にROIを設定し時間放射能曲線を得た．さらに静注1分後と30分後の静態像を撮像した．

結果は^{99m}Tc-HMPAO肺シンチ上，24兎中20兎（83.3%）に照射側肺に異常集積（対側健常肺より高い集積）を認めた．そのうち，照射24時間後では10兎中9兎（90%）に異常集積を認めた．また時間放射能曲線から^{99m}Tc-HMPAOの集積動態をみると静注直後のピーク比は不定であるが，1分後には既に照射側肺は対側肺に比し集積が高く，30分後にはさらに集積比は増大した．また^{99m}Tc-HMPAOの異常集積を認めた12兎で^{99m}Tc-MAAシンチを施行したが，そのうち9兎（75%）に肺動脈血の低下を認めた．

一方，胸部単純X線写真では照射側肺に異常陰影を認めず，病理組織像でも対側健常肺と比較して変化を指摘し得なかった．しかし電顕像では血管内皮細胞の浮腫状変化と空胞変性を認めた．なお遊離した$^{99m}TcO_4^-$が集積した可能性を考え，$^{99m}TcO_4^-$による肺シンチと単純な血管外組織への拡散，蓄積を考え^{99m}Tc-DTPA肺シンチも施行したがいずれも異常集積を認めなかった．

放射線照射肺への^{99m}Tc-HMPAO集積の詳細なメカニズムについてはさらに検討する必要があるが，^{99m}Tc-HMPAOは，胸部X線単純写真や組織像で変化を認めがたい放射線照射後早期の家兎肺に高率に異常集積を示し，肺血管内皮細胞障害を反映するトレーサとなり得る可能性が示唆された．

ABSTRACT

The pulmonary microvascular endothelium manifests structural and functional alterations following irradiation. It is important to determine a suitable method for detecting the endothelial damage. For the assessment of the initial phase of this pulmonary injury, ^{99m}Tc-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) scintigraphy as an indicator of early endothelial injury induced by irradiation was employed. Japanese white rabbits were exposed to 50 Gy irradiation toward the hemithorax, and ^{99m}Tc-HMPAO scintigraphy was performed at 24 hrs, 2 days, 14 days. and 28 days following irradiation. Twenty of 24 rabbits (83.3%) showed abnormal ^{99m}Tc-HMPAO uptake in the irradiated lung during this period. Of 10 rabbits examined 24 hrs after irradiation, nine (90%) already showed abnormal ^{99m}Tc-HMPAO uptake. The time-activity curves revealed that high uptake of this agent occurred rapidly within the first 1 min after injection. Chest radiography in all these 20 rabbits with abnormal ^{99m}Tc-HMPAO uptake exhibited no abnormal opacity. Histological studies performed in 7 of these 20 rabbits revealed no remarkable changes in the irradiated lung compared to the contralateral non-irradiated lung, while electron microscopic study showed scattered vacuolation and edematous changes in the endothelium. These results indicate that ^{99m}Tc-HMPAO scintigraphy may detect early lung microvascular endothelial injury induced by irradiation.

INTRODUCTION

The pulmonary capillary endothelial bed is thought to be the most important initial site of irradiation-induced injury in the lung and an etiologic factor in consequent radiation pneumonitis. An ultrastructural study of the development of radiation injury revealed that the first sign of pulmonary damage appeared in the endothelium[1)-3)]. The increased vascular permeability that occurs as a consequence of these endothelial damages has been investigated by radiotracer methods using ^{99m}Tc-HSA or ^{99m}Tc-DTPA[4),5)]. However, these methods do not seem to detect early endothelial damage. The brain perfusion agent, ^{99m}Tc-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO)[6)], has also been used for tumor scintigraphy, mainly in the thoracic region[7)-9)]. Suga et al [10)] reported the application of this agent for thoracic tumors, and they frequently observed intense pulmonary uptake of this agent corresponding to the irradiated field, in the absence of findings of radiation pneumonitis on chest computed tomography. It is therefore suggested that this agent may be of value for detecting early radiation pulmonary injury. Accordingly, the present study was conducted to investigate the value of ^{99m}Tc-HMPAO scintigraphy for the early detection of irradiation-induced pulmonary microvascular endothelial injury. An experimental animal model was used, in which minimal pulmonary vascular lesions developed following a single dose of 50 Gy irradiation.

MATERIALS AND METHODS

(1) Animals and irradiation

Twenty-four Japanese white rabbits weighing 2.5-3.5 kg were anesthetized with 50 mg kg^{-1} Nembutal administered intravenously via the ear vein. Irradiation was performed through a right anteiror chest field of 5.0×2.5 cm, with a single 50 Gy dose, using 200 keV X-ray with a h. v. l. of 1.28 mm Cu and 1 mm Al. The irradiated region included the right lung and right hemimediastinum, but not the left lung field. The relatively high dose of 50 Gy was selected, as previous investigators[11)]

had reported the difficulty of producing exudative radiation pneumonitis in rabbits compared to rats and mice. In addition, Hermann et al.[12] reported that ^{99m}Tc-MAA lung scintigraphy in rabbits receiving a single 50 Gy dose of radiation showed reduced uptake.

(2) ^{99m}Tc-HMPAO Scintigraphy

The anesthetized rabbits were fixed symmetrically in the supine position over a detector with a collimator, and received a bolus injection of 37 MBq (1 mCi) ^{99m}Tc-HMPAO via the ear vein. Posterior sequential lung images were taken at one frame per sec for 1 min immediately following injection, and subsequent images were obtained at one frame per min for 30 min, using a low-energy collimator attached to a gamma camera (TOSHIBA GCA 901-A). The early image was obtained by summation of the first 1 minute, and the delayed image was obtained by summation of frames during the last 5 min (Fig. 1). A 20% window centered on the 140 keV photo-peak was used for each view.

In all 24 rabbits receiving a single 50 Gy dose of radiation, ^{99m}Tc-HMPAO scintigraphy was performed at the following times: 10 rabbits at 24 hrs after irradiation, 5 after 2 days, 5 after 14 days, and 4 after 28 days.

Time-activity curves were obtained by setting square regions of interest (ROI) with a size of 4×4 pixels in the lower lung field in both the irradiated and the contralateral non-irradiated lung. Quantitative evaluation of ^{99m}Tc-HMPAO uptake in the irradiated lung was expressed as the mean count ratio per pixel of the irradiated side over that of the contralateral side (^{99m}Tc-HMPAO uptake ratio).

(3) ^{99m}Tc-MAA Scintigraphy

To investigate the changes in pulmonary perfusion after irradiation and to compare the results with those of ^{99m}Tc-HMPAO scintigraphy, ^{99m}Tc-MAA perfusion images were obtained 4 days before or after the ^{99m}Tc-HMPAO examination in 12 irradiated rabbits. A dose of 37 MBq (1 mCi) of ^{99m}Tc-MAA was injected intravenously, and posterior static images were obtained at 5 min after the injection. The ROI sets were the same as those for ^{99m}Tc-HMPAO scintigraphy. When the mean count per pixel of the irradiated lung was reduced by more than 20% compared with that in the contralateral non-irradiated lung. The pulmonary perfusion was considered to be reduced. When the difference was within 20%, the blood flow was considered to be unchanged.

(4) $^{99m}TcO_4^-$ and ^{99m}Tc-DTPA Scintigraphy

In addition, $^{99m}TcO_4^-$ and ^{99m}Tc-DTPA (^{99m}Tc-diethylene triaminepenta acetic acid) scintigraphy was performed in rabbits with abnormal ^{99m}Tc-HMPAO uptake in the irradiated lung. $^{99m}TcO_4^-$ scintigraphy was conducted to exclude the possibility of accumulation of free $^{99m}TcO_4^-$ released from ^{99m}Tc-HMPAO. ^{99m}Tc-DTPA scintigraphy was performed to investigate whether vascular permeability and the extravascular space were increased in the irradiated lung. These scintigraphic findings were compared with the findings of ^{99m}Tc-HMPAO scintigraphy. Both of these scintigraphies were performed in 6 rabbits 4 days after the ^{99m}Tc-HMPAO examination. A does of 37 MBq (1 mCi) of $^{99m}TcO_4^-$ or ^{99m}Tc-DTPA was injected intravenously, and the images were obtained in the same manner as for ^{99m}Tc-HMPAO examination.

(5) Chest radiographic and histological observations

Chest radiography was performed in all rabbits after the ^{99m}Tc-HMPAO examinaition to observe whether there was abnormal opacity. Seven rabbits with abnormal ^{99m}Tc-HMPAO uptake in the

irradiated lung were killed at the following times : 3 rabbits were killed 24 hrs after irradiation, one after 2 days, and 3 after 28 days. Histological examination of hematoxylin and eosin-stained specimens was then performed to estimate the degree of lung injury caused by irradiation in all 7 rabbits.

Electron microscopic observations were also performed in 4 of the above-mentioned 7 rabbits. Among those 4 rabbits, 2 were killed 24 hrs after irradiation, one after 2 days, and one after 28 days.

RESULTS

^{99m}Tc-HMPAO scintigraphy performed 24 hrs to 28 days after irradiation showed abnormal ^{99m}Tc-HMPAO uptake in the irradiated lung in 20 of the 24 rabbits (83.3%). Of 10 rabbits examined 24 hrs after irradiation, 9 (90%) showed abnormal uptake in the irradiated lung (Fig. 1). Of 5 after 2 days, 4 (80.0%) showed abnormal uptake. Of 5 after 14 days, 4 (80.0%) showed abnormal uptake. Of 4 after 28 days, 3 (75.0%) showed abnormal uptake.

In all the 20 rabbits that showed abnormal uptake of ^{99m}Tc-HMPAO, the time-activity curves revealed that a high uptake of this agent occurred within the first 1 min immediately after the injection (Fig. 2). However, the maximum value for the ^{99m}Tc-HMPAO uptake ratio was observed 30 minutes after the ^{99m}Tc-HMPAO injection (Fig. 3).

Pulmonary perfusion, assessed by ^{99m}Tc-MAA scintigraphy in 12 rabbits with abnormal accumulation of ^{99m}Tc-HMPAO, was unchanged compared to the contralateral side in 3 (25%) rabbits and had decreased in 9 (75%) (Fig. 4). Chest radiography, performed in all of the 20 rabbits that showed abnormal uptake in ^{99m}Tc-HMPAO scintigraphy 24 hrs to 28 days after irradiation, did not show any abnormal opacity in the irradiated lung (Fig. 5). Histological observations made with a light microscope did not reveal any significant changes of pulmonary peripheral structure compared to the contralateral non-irradiated lung (Fig. 6). There was no obvious thickening of the interalveolar septa or exudative changes within the alveolar spaces.

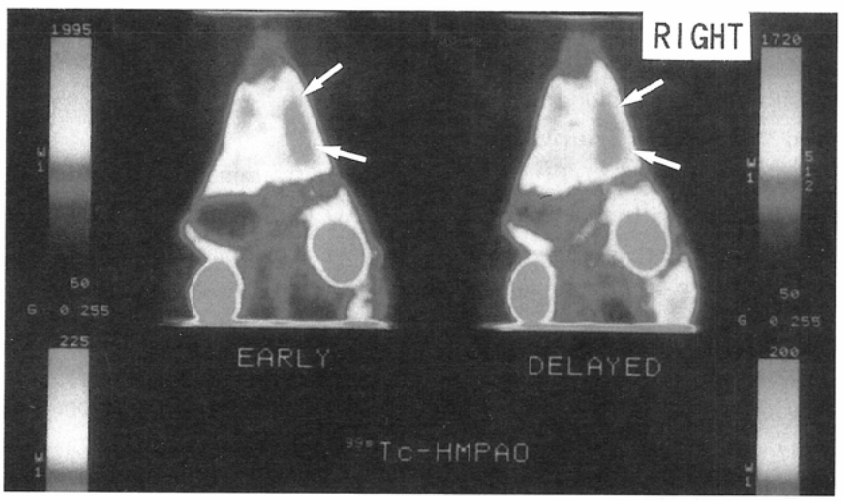


Fig. 1 ^{99m}Tc-HMPAO scintigraphy in a rabbit receiving 50 Gy irradiation 24 hrs previously : Both early (1 min) and delayed (30 min) images show more intense activity (arrows) of ^{99m}Tc-HMPAO in the irradiated right lung than the contralateral non-irradiated side.

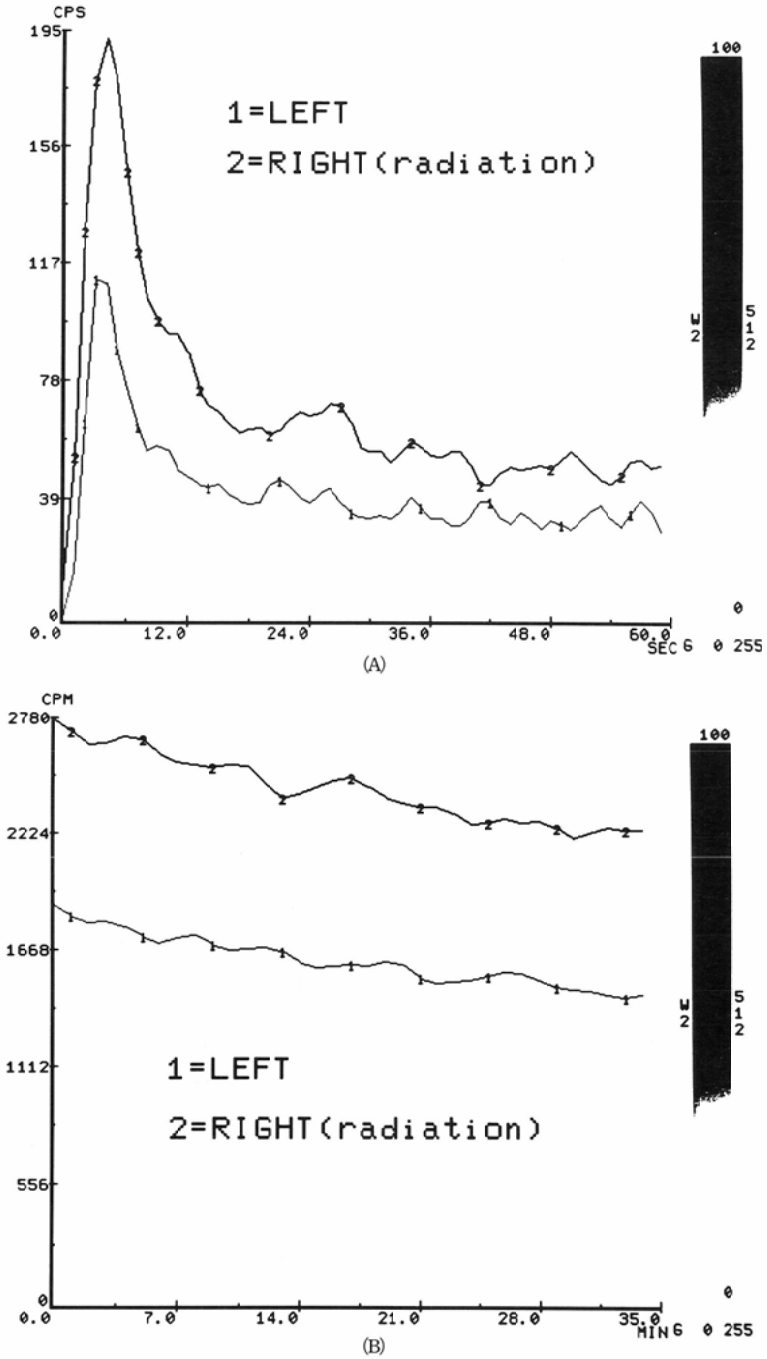


Fig. 2 Time-activity curves obtained from ^{99m}Tc-HMPAO scintigraphy in Fig. 1.

(A) Time-activity curve for the first 1 min immediately after injection revealing higher ^{99m}Tc-HMPAO uptake in the irradiated lung (right)

(B) Time-activity curve for 30 min after injection, showing a persistent higher uptake in the irradiated lung than the contralateral non-irradiated lung

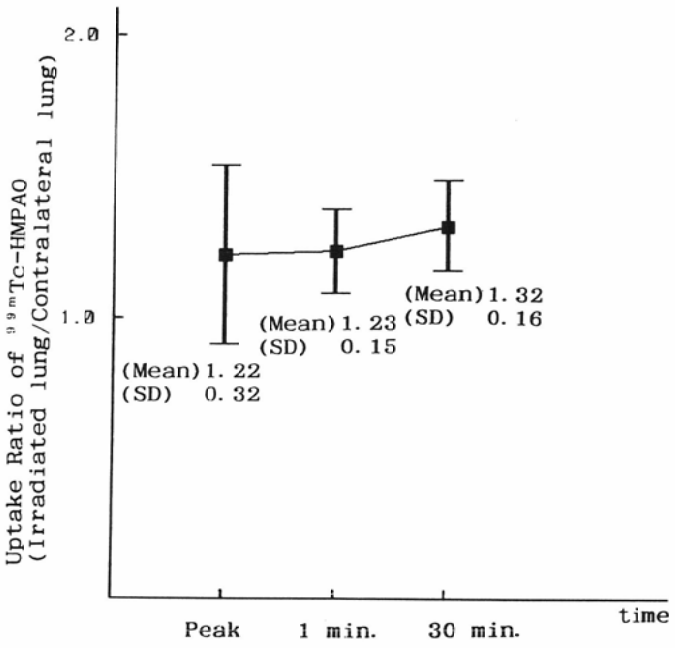


Fig. 3 Kinetics of ^{99m}Tc-HMPAO; Changes of irradiated/contralateral lung ratios of ^{99m}Tc-HMPAO activity after injection in all the 20 rabbits that showed abnormal uptake of ^{99m}Tc-HMPAO. This figure reveals that a high uptake of ^{99m}Tc-HMPAO occurs within the first 1 min immediately after injection, and the maximum value for ^{99m}Tc-HMPAO uptake ratio is observed 30 min after injection.

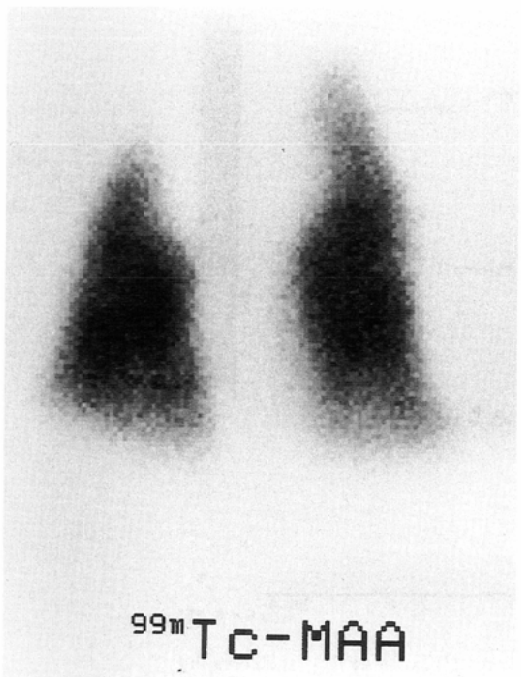


Fig. 4 ^{99m}Tc-MAA perfusion scintigraphy of the same rabbit shown in Fig. 1 did not show a reduced uptake in the irradiated right lung. Because the difference in mean counts per pixel of the irradiated lung compared with that of the non-irradiated lung is within 20%, the pulmonary perfusion is considered to be unchanged.

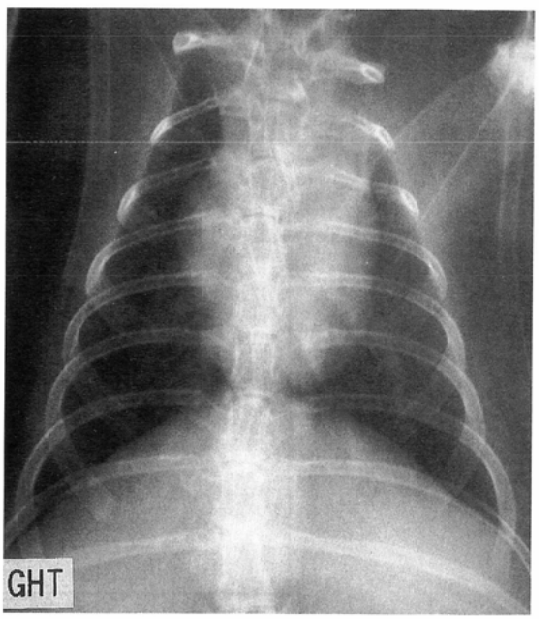


Fig. 5 Chest radiograph 24 hrs after irradiation showing no abnormal opacity in the irradiated right lung

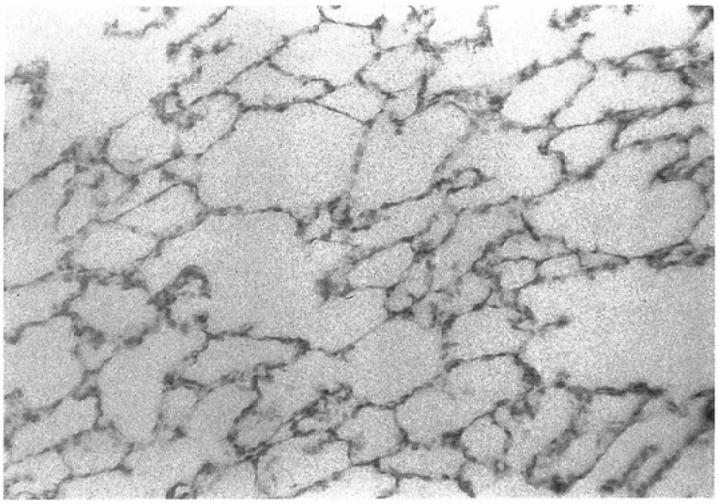


Fig. 6 Light microscopic histological appearance of irradiated lung 2 days after irradiation showing no remarkable changes compared to the contralateral non-irradiated lung (hematoxylin and eosin stain)

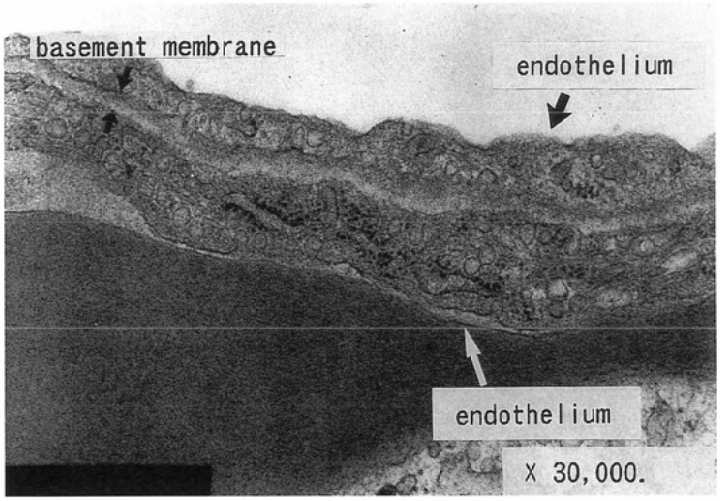
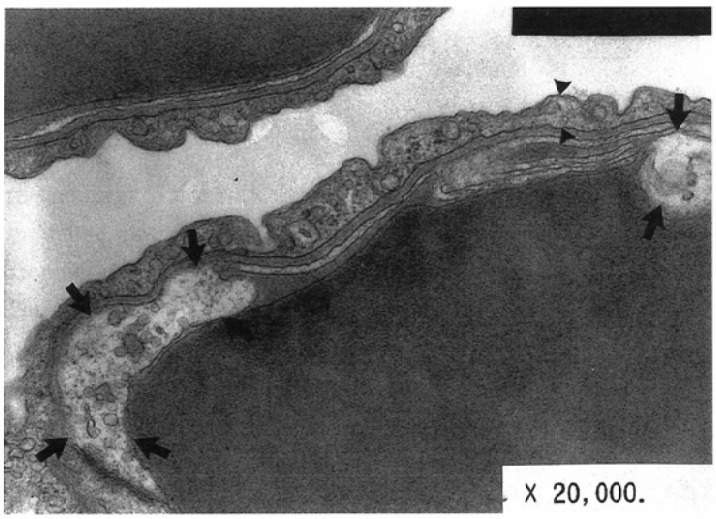


Fig. 7
(A) Electron microscopic appearance of the lung of a control rabbit



(B) Electron microscopy of irradiated lung 2 days after irradiation showing edematous change of the microvascular endothelium and vacuolation (arrows) in the endothelium. No obvious alterations are observed in other structures such as epithelial cell (arrowheads) and basement membrane.

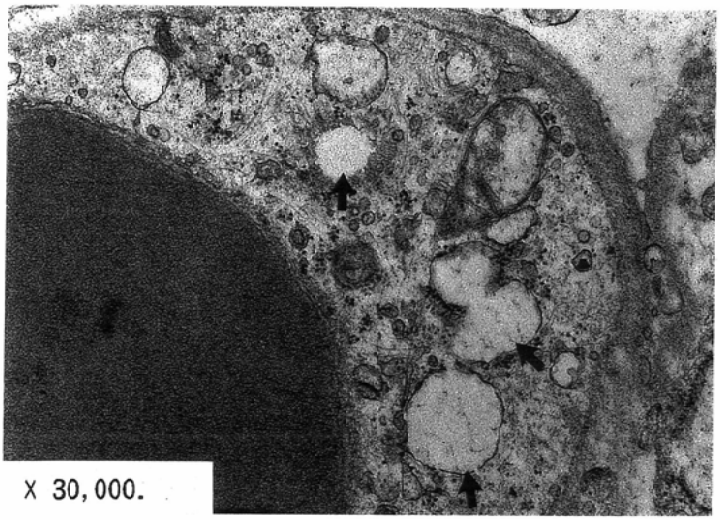


Fig. 7
(C) In the same rabbit shown in Fig. 7 (B), there are many vacuole (arrows) within the endothelium and edematous swelling.

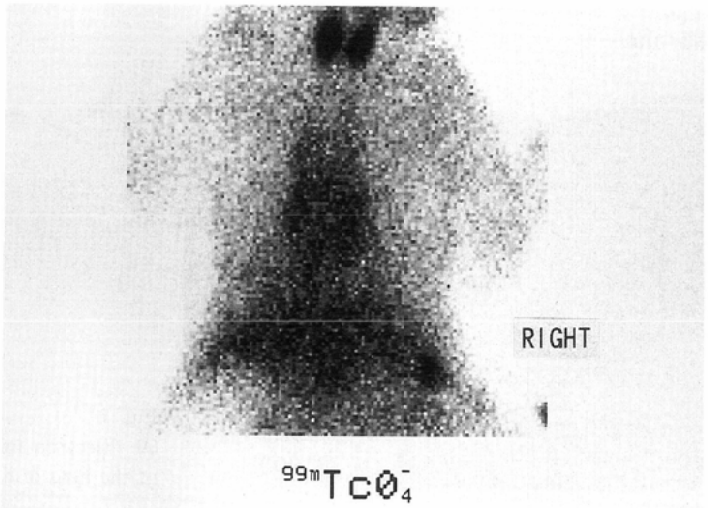
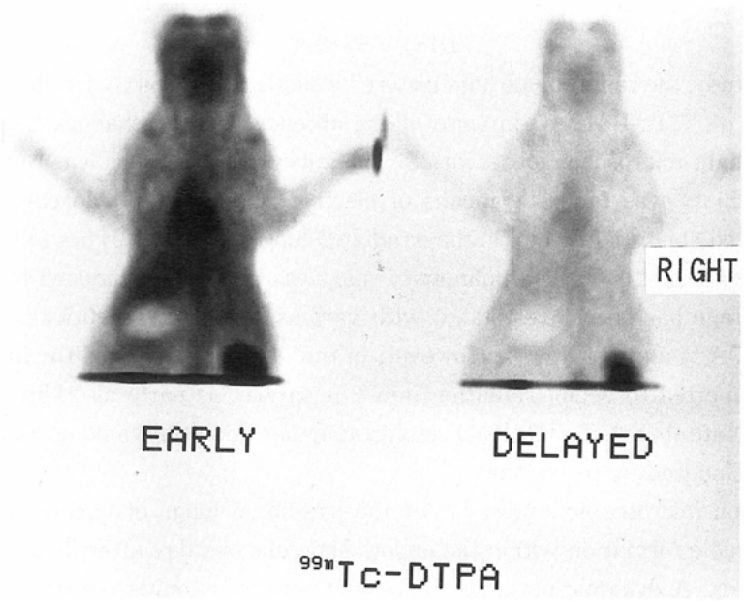


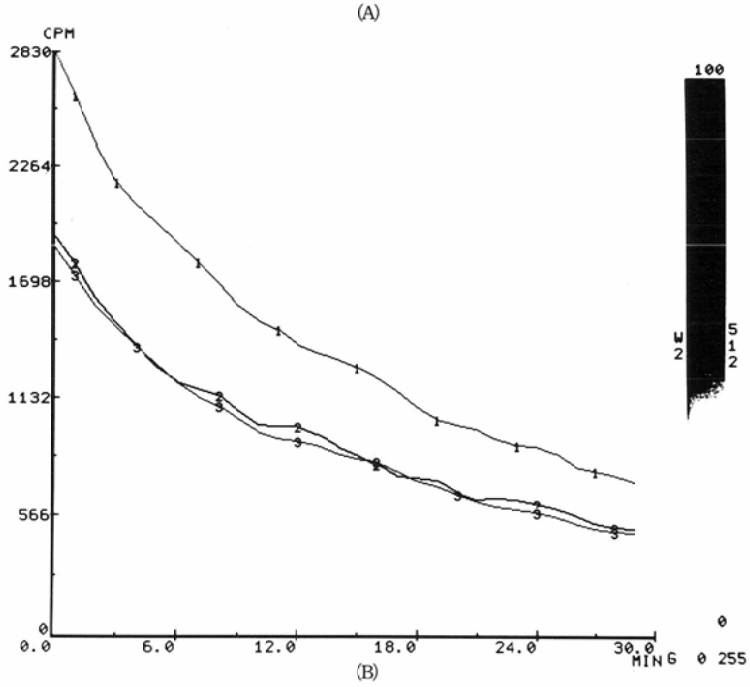
Fig. 8 $^{99m}TcO_4^-$ scintigraphy performed in the rabbit with showing high ^{99m}Tc-HMPAO uptake in the irradiated lung (right). This image showing no abnormal uptake in the irradiated lung compared with the contralateral non-irradiated lung.

However, electron microscopic observation revealed degeneration of the microvascular endothelium ; this was manifested as scattered vacuoles or blebs within the endothelium and edematous swelling. These changes were not widespread, and no obvious alterations compared with the normal lung were noted in other structures such as epithelial cells, interstitium, or basement membrane (Fig. 7).

Neither $^{99m}TcO_4^-$ nor ^{99m}Tc-DTPA scintigraphy showed any abnormal uptake in the irradiated lung of any of the 6 rabbits examined. The activity in the irradiated lung did not differ from that of the contralateral non-irradiated lung (Figs. 8, 9). Neither of the time activity curves showed any significant differences between the irradiated and non-irradiated contralateral lungs (Fig. 9-B).



(A)



(B)

Fig. 9

(A) ^{99m}Tc-DTPA scintigraphy showing no abnormal accumulation in the irradiated lung in the both early (5 min) and delayed image (30 min)

(B) Time-activity curve obtained during 30 min after injection also showing no significant difference between in the irradiated and contralateral lung

1 : heart, 2 : left, 3 : right (irradiated lung)

DISCUSSION

In the present study, the rabbit lungs administered a single dose of 50 Gy irradiation demonstrated abnormal uptake of ^{99m}Tc-HMPAO in spite of the absence of clear changes in the lung on chest radiography and light microscopic observation. The injury of these lungs was relatively slight, and only endothelial injury was found by means of electron microscopy. Moreover, ^{99m}Tc-HMPAO scintigraphy showed abnormal uptake in the irradiated lung as early as 24 hrs following irradiation, with a high incidence (90.0%). The pulmonary microvascular injury induced by irradiation at a relatively early stage has been investigated with various radiopharmaceuticals, such as Gallium-67[13),14)], ^{99m}Tc-DTPA[15)], and ^{123}I-IMP[16)]. However, in the author's survey of the literature, no other agent has been reported to depict radiation injury positively as early as 24 hrs after irradiation. These results indicate that ^{99m}Tc-HMPAO scintigraphy has potential value as an indicator of early pulmonary injury induced by irradiation.

Previous electron microscopic studies[1)–3)] of the irradiated lungs of various animals have also demonstrated vacuole formation within the endothelial cells one day after irradiation, as observed in the present study. A dynamic progression to radiation pneumonitis occurred during the 2 to 6 month period after irradiation[1),3)]. ^{99m}Tc-HMPAO, which showed abnormal uptake in these lungs with endothelial injury, was probably considered to indicate abnormal kinetics in relation to the endothelial injury. ^{99m}Tc-HMPAO is thought to accumulate within the injured endothelium, because this agent, a lipophilic substance with a molecular weight of 380 Da[17)], can penetrate into the endothelial cytoplasm through the pores in the cell membrane. This characteristic has been widely employed in the labelling of WBC and platelets with this agent[18)–20)]. Kawakami et al [17)] demonstrated the intracellular transfer of this agent in the alveolar epithelium in an aerosol study. Considering the ^{99m}Tc-HMPAO kinetics indicating abnormal uptake, the higher irradiated/contralateral lung uptake ratio during 60 sec after ^{99m}Tc-HMPAO injection occurred rapidly after the injection (Fig. 2). It seems that this rapid manifestation of abnormal uptake in the injured lung is characteristic of this agent. The enhanced permeability of the radiation-damaged endothelial membrane to ^{99m}Tc-HMPAO contributes to the rapid manifestation of abnormal uptake of this agent.

^{99m}Tc-MAA scintigraphy revealed that the pulmonary blood flow tended to be reduced following irradiation. The incidence of reduced pulmonary perfusion (75.0%) was lower than the positive incidence (83.3%) on ^{99m}Tc-HMPAO scintigraphy. These results indicate that ^{99m}Tc-HMPAO scintigraphy was more sensitive for detecting pulmonary injury than ^{99m}Tc-MAA scintigraphy. Comparison between ^{99m}Tc-MAA and ^{99m}Tc-HMPAO scintigraphic findings also suggested that ^{99m}Tc-HMPAO could reach the peripheral pulmonary areas which ^{99m}Tc-MAA could not reach. It is considered that ^{99m}Tc-HMPAO, with its low molecular weight of 380 Da, can reach the peripheral lung which the large ^{99m}Tc-MAA, with a size of 30-50 μm[21)], cannot reach.

The time-activity curves also revealed that the ratio of ^{99m}Tc-HMPAO uptake in the irradiated lung to the contralateral normal lung increased with time after injection. This finding indicates slow washout of this agent from the irradiated lung following high uptake (Fig. 2, 3). Reduced pulmonary blood flow observed on ^{99m}Tc-MAA scintigraphy could be responsible for this slow washout. Moreover, it is possible that the nature of ^{99m}Tc-HMPAO was changed from lipophilic to hydrophilic

within the endothelial cell, and that this agent was retained there, as has been demonstrated in brain tissue[22].

On the other hand, in rabbits showing positive ^{99m}Tc-HMPAO uptake in the irradiated lung, ^{99m}Tc-DTPA scintigraphy showed neither abnormal uptake nor different kinetics in the irradiated lung compared to the non-irradiated lung. The hydrophilic agent ^{99m}Tc-DTPA transfers across capillaries through the inter-endothelial pores into the extravascular interstitial space as a result of enhanced microvascular permeability or increased extravascular space[5),15),17]. Negative results with this agent indicated that neither of these features was involved in this relatively early stage of pulmonary injury. The present light and electron microscopic findings also suggested that there was no increase in the extravascular space such as thickening of the interstitium or infiltration within the alveolar space. In addition, the negative results of $^{99m}TcO_4^-$ scintigraphy suggested that the abnormal uptake shown on ^{99m}Tc-HMPAO scintigraphy was not due to nonspecific accumulation of free $^{99m}TcO_4^-$ released from ^{99m}Tc-HMPAO[23)–25)].

Thus, from the results of the present study, it is considered that the high ^{99m}Tc-HMPAO uptake in the irradiated lung may be related to endothelial injuries such as enhanced permeability of the endothelial cell membrane. However, to clarify the precise mechanism responsible for the high ^{99m}Tc-HMPAO uptake in the irradiated lung, further investigations using microautoradiography are necessary.

A diffuse high uptake of ^{99m}Tc-HMPAO has been reported in scintigraphies of smokers' lungs by Shih et al [26]. They suggested that the high uptake of this agent reflected endothelial damage due to substances contained in cigarette smoke. The present results and this finding in the smoker's lung suggest that abnormal accumulation of ^{99m}Tc-HMPAO may indicate nonspecific endothelial damage. However, the nonspecificity of the pulmonary uptake of this agent does not diminish the importance of ^{99m}Tc-HMPAO scintigraphy, since this method may provide considerable information of importance in the early management of radiation-induced tissue damage. Earlier detection of pulmonary damage induced by irradiation would allow administration of higher doses of radiation to the lung without subsequent severe injury.

In conclusion, ^{99m}Tc-HMPAO scintigraphy, which showed abnormal uptake as early as 24 hrs after irradiation, appears to be a sensitive indicator of pulmonary microvascular injury induced by irradiation. Further study, however, is necessary to clarify the precise mechanism responsible for this high uptake.

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