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Prolonged lung retention of ^{123}I-IMP in pulmonary fibrosis

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We compared radiographic findings and the retention of N-isopropyl-p[^{123}I]-iodoamphetamine (^{123}I-IMP) in 23 patients with pulmonary fibrosis. During the 30 minutes following a rapid injection of 55.5 MBq of ^{123}I-IMP into the antecubital vein, the image of regional activity was stored. After this, 185 MBq of ^{99m}Tc-MAA was injected and its image was stored to determine the region of interest. The half time ($T_{1/2}$) of ^{123}I-IMP release from the lung was calculated in each pixel between 10 and 25 minutes after the injection. Chest roentgenograms were taken, and the lung field was divided into 6 portions (right upper, middle and lower, and left upper, middle and lower). A quantitative score was assigned to the radiographic finding (X-ray score). The $T_{1/2}$ values in the above patients were longer than the $T_{1/2}$ values in normal subjects. Prolonged $T_{1/2}$ values were observed in the lung fields which had high X-ray scores. The X-ray scores and the $T_{1/2}$ values in corresponding areas had a positive relation.

Key words: ^{123}I-IMP, lung dynamic scintigraphy, pulmonary fibrosis

INTRODUCTION

IT HAS BEEN WELL ESTABLISHED that the lung selectively takes up and metabolizes biogenic amines.[1–5] In recent years the movement of radioactive amines in the lung has been studied and their clinical application has been reported.[6–12] N-isopropyl-p[^{123}I]-iodoamphetamine (^{123}I-IMP) was developed for the purpose of evaluating regional brain blood flow.[13] Since then, its high accumulation in the lungs has been observed.[8–10] We previously reported that the lung release of ^{123}I-IMP was delayed in interstitial lung diseases.[11] It has been reported that injected ^{123}I-IMP accumulated in the alveolar space and adsorbed to the alveolar cells.[14,15] The uptake of ^{123}I-IMP in patients with chronic obstructive pulmonary disease has also been investigated.[10] The analysis of the lung release of ^{123}I-HIPDM was proposed as a new lung dysfunction index.[7] We believe that a new index for the clinical evaluation of pulmonary diseases might be derived by analyzing amine movement in the lung. We analyzed the lung release of ^{123}I-IMP in pulmonary fibrosis and compared it with chest roentgenogram findings in this study.

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SUBJECTS

Eight normal volunteers (all male, 5 nonsmokers and 3 smokers) and 23 patients with the pulmonary fibrosis were examined. The diagnosis was determined by chest X-ray photographic findings, lung function tests, and bronchoalveolar lavage examination. Half or one year later, six patients were examined a second time in a follow-up examination.

MATERIALS AND METHODS

A. Lung dynamic scintigraphy

55.5 MBq of ^{123}I-IMP (0.225 mg) was rapidly ininjected into the antecubital vein. During the 30 minutes immediately following the injection, data were acquired at a rate of 3 frames/minute in a 32×32 matrix. After taking this measurement, 185 MBq of ^{99m}Tc macroaggregated albumin (^{99m}Tc-

MAA) was then injected and the image was stored. Throughout these consecutive measurements, the patients lay quietly in a supine position.

The region of interest (ROI) was defined by the ^{99m}Tc-MAA image using a 25% window.

The decrease in pulmonary ^{123}I-IMP was expressed by a multiple exponential equation. However the time-activity curve $C(t)$ over the 30 minutes (Fig. 1) was quite closely approximated by a 2 component equation (equation 1).

$$C(t)=C_1*\exp(-ke_1*t)+C_2*\exp(-ke_2*t) \quad (1)$$

About 5 minutes (frame 15) after the injection, $C(t)$ was mostly described by the second component ($C_2*\exp(-ke_2*t)$). Therefore, as in a previous study,[11] we analyzed the second component in this study. The initial activity (C_2) and the time-constant (ke_2) were calculated by the least squares method between 10 and 25 minutes (between frames 30 and 75) after the injection of ^{123}I-IMP, and the half-time ($T_{1/2}$) was calculated from (ke_2) (equation 2).

$$T_{1/2}=(\ln 2)/ke_2 \quad (2)$$
$$T_{1/2}=0.6931/ke_2$$

(ke_2) and ($T_{1/2}$) were calculated in each pixel. This analytic method has already been reported.[11]

To compare with chest roentgenogram findings, the ROI was divided into 6 portions (right upper, middle and lower, and left upper, middle and lower), and the average $T_{1/2}$ value in each region was calculated.

B. Chest roentgenogram findings

A chest roentgenogram was taken, and the lung field was divided into 6 portions (right upper, middle and lower, and left upper, middle and lower). A quantitative score was assigned to the radiographic finding in each lung field (X-ray score). Crystal et al.[16,17] reviewed the evaluation of roentgenograms. Chest roentgenogram early in the course of the disease showed localized linear, nodular or ground-glass patterns. With the progression of the disease, nodular or reticulonodular patterns began to appear. In later stages, the patterns changed to a coarse reticular pattern with cystic areas, and then finally to a honeycomb appearance. In this review, we assigned the score for chest roentgenograms according to the following criteria:

0: normal;
1: small nodular, fine reticular, or ground glass shadow;
2: nodular, reticulonodular shadow;
3: reticular shadow with cyctic change;
4: honeycombing.

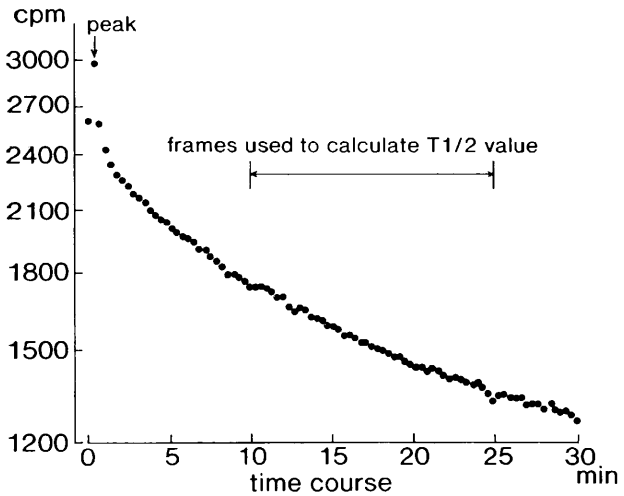

Fig. 1 The time activity curve in the lung field. The count is average of pixel in ROI.

RESULTS

Figure 2 shows the $T_{1/2}$ value for each pixel in the case of both a patient and a normal subject. The $T_{1/2}$ values for the patient were longer than those

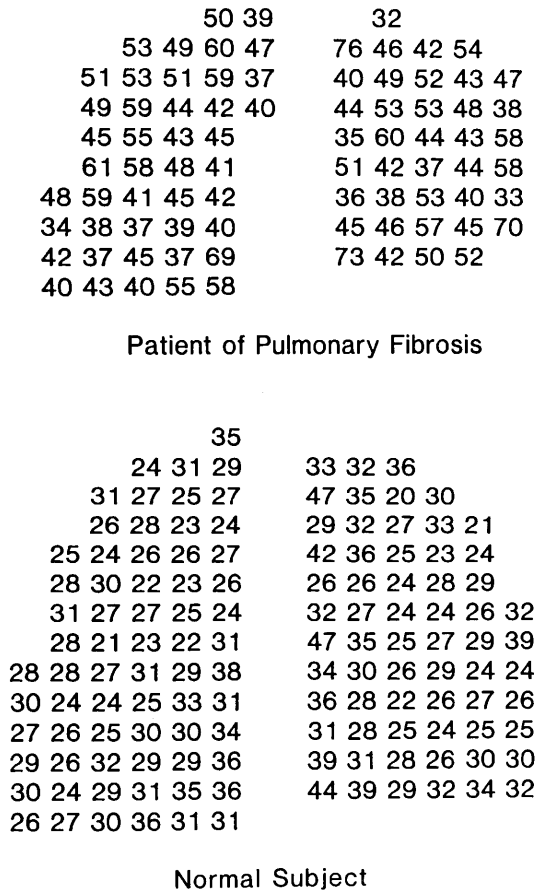

Fig. 2 The distribution of $T_{1/2}$ values (minutes) in the case of patient and a normal nonsmoker.

Table 1 Distribution of the half times in normal subjects

	Half time (min)									
	20–	25–	30–	35–	40–	45–	50–	55–	60–	65–
Non-smoker										
1		4	40	30	11	13	2			
2	2	34	34	26	4					
3		4	51	33	11					
4		22	44	22	5	5	2			
5		2	17	63	17					
mean		13	37	35	10	4	1			
Smoker										
1			28	21	23	18	3	8		
2			19	32	35	10	3			
3		9	27	27	27	9				
mean		3	25	27	28	12	2	3		

The halftime is divided into five minute intervals, and the number indicates the percent number of pixel included in each interval.

Table 2 Distribution of the half times in pulmonary fibrosis

	Half time (min)														
Patient	20–	25–	30–	35–	40–	45–	50–	55–	60–	65–	70–	75–	80–	85–	90–
1	83	24	2	2											
2	17	46	27	6	2	2									
3	37	46	14	3											
4		20	60	20											
5		29	51	7	9	4									
6		12	46	27	12		2								
7	3	25	48	20				3	3						
8	5	31	29	18	6	8	1	1	1						
9	2	17	21	30	23	8	6	5	2			2			2
10		10	39	20	18	4	4	2		2		2			
11		16	27	32	11	7	2	5							
12		5	26	34	15	5	5	10			2				
13		7	36	31	17	3	3	2		2					
14			15	34	10	12	15	2	5				7		
15		4	17	12	40	6	4	6	8		2	2			
16			4	14	28	20	16	13	4	1	1				
17		6	9	20	18	20	9	9	4		4	2			
18		8	18	28	22	8	6	2	4	4	2				
19			13	28	35	9	6	1	4	3	1				
20		6	17	20	20	17	9	3	3	2	3	2			
21			5	18	19	21	14	9	10	3			1		
22		2	6	21	28	11	13	4	6				6	2	2
23			2	10	12	13	16	12	2	5	7	8	2	3	10

for the normal subject. Tables 1 and 2 show the frequency of $T_{1/2}$ values over the specified time at 5 minute intervals. The numbers appearing in the table show the percentage of pixel $T_{1/2}$ values within each 5 minute period. Because the number of pixels in ROI differed from subject to subject, we normalized the number of pixels by using the percentage. Table 1 and Table 2 show the results for normal subjects and patients, respectively. The $T_{1/2}$ values were distributed between 25 and 39 minutes in normal nonsmoker subjects. The $T_{1/2}$ values were slightly greater in smokers than those in nonsmokers, and the $T_{1/2}$ values in patients were greater than in normal subjects. The duration of the $T_{1/2}$ value was different in each lung field.

Figure 3 shows the relation between the $T_{1/2}$ values and the chest X-ray score in corresponding areas. The $T_{1/2}$ values are greater in the lung fields

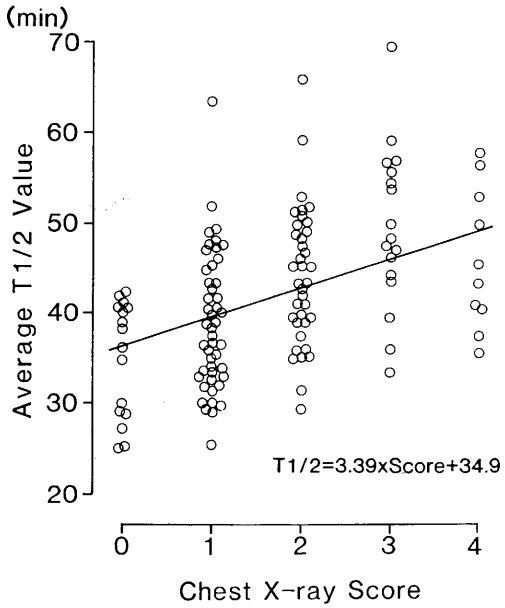

Fig. 3 The relation between the chest X-ray score and the $T_{1/2}$ value. The $T_{1/2}$ values in score "2", "3", and "4" areas are longer than those in score "0" areas ($p<0.01$, by Spearman's test). The $T_{1/2}$ values in score "2" and "3" areas are longer than those in score "1" areas ($p<0.05$).

Table 3 Comparison of chest X-ray results at follow-up examination (Score 2 category)

		Chest X-ray finding	
		No change	Worse
$T_{1/2}$ value (minutes)	42>	11	4
	42<	3	8

$p<0.05$, χ^2 test
The lung fields were divided to two classes according to their $T_{1/2}$ value. This division at 42 minutes was determined from the regression line (Fig. 2). Each number represents the number of lung fields.

with higher chest X-ray scores (by Spearman's test, $p<0.05$). The chest X-ray score and the average $T_{1/2}$ value had a positive correlation ($r=0.64$, $p<0.05$).

The results of the follow-up study in 6 patients are listed in Table 3. The changes in the chest X-ray score and the average $T_{1/2}$ value had a statistically significant relation in the χ^2 (chi square) test.

DISCUSSION

The metabolization of ^{123}I-IMP was a problem in this study. However, it has been reported that 20% of IMP was converted to p-iodoamphetamine (PIA) within 2 hours after administration and the remaining IMP is not metabolized.[18] Because our examination of each subject was completed within about 30 minutes, it is likely that a large percentage of ^{123}I was still present as ^{123}I-IMP or ^{123}I-PIA during our examination.

We had hypothesized that the increase in the number of cells resulting from pulmonary fibrosis could be estimated by analyzing ^{123}I-IMP washout from the lung. Since there was a relation between the chest X-ray score and the $T_{1/2}$ value, this confirms that the delay in ^{123}I-IMP washout from the lung was related to the stage of pulmonary fibrosis. However, the extent of the prolongation at each stage differed among patients who had identical X-ray scores, and the $T_{1/2}$ value distribution for each chest X-ray score was diffused. We feel that it is difficult to assess the stage of pulmonary fibrosis from the $T_{1/2}$ value only.

We tested the usefulness of this method for following up patients with pulmonary fibrosis. Because there was only a sufficient number of lung fields with a score "2" in the 6 follow-up patients for the purpose of statistical analysis, we only compared these areas. Those lung fields with a greater $T_{1/2}$ value despite a lower chest X-ray score, were impaired within 1 year (Table 3). It has been reported that in the midcourse of the disease, roentgenograms were not as reliable as physiologic and morphologic evaluations in gauging the severity of the disease and the degree of fibrosis.[16,17] This is because the radiographic correlate of the fibrotic process can be masked by concomitant alveolitis. We consider that the analysis of ^{123}I-IMP washout from the lung can show the activity of pulmonary fibrosis and is a useful new index for following up patients.

Early reports concerning the movement of ^{123}I-IMP in the lung referred only to endothelial cell function. However, we previously reported that injected ^{123}I-IMP moved to the alveolar space and was adsorbed to the alveolar macrophage.[14] The distribution of ^{123}I-IMP in the alveolar wall cells measured by autoradiography has also been reported.[15] It is certain that the alveolar macrophage contains the binding site for ^{123}I-IMP. On this basis, we previously studied prolonged ^{123}I-IMP retention in interstitial lung diseases.[11] We considered that ^{123}I-IMP was adsorbed to the inflammatory granulome and to the increased alveolar macrophage. The increase in the number of alveolar macrophages in smokers is well known. Therefore, slight prolongation of the $T_{1/2}$ value in the normal smokers is thought to indicate an increase in the number of alveolar macrophages.

The adsorption site of ^{123}I-IMP on the alveolar macrophage has not been confirmed. However, it has been reported that amphetamine binds to mixed

function oxidase (MFO) and that alveolar macrophage contains MFO.[19] Furthermore it has been reported that the fibroblast contains the monoamine oxidase (MAO) and that MAO increases in bleomycin induced pulmonary fibrosis.[20,21] Also, amphetamine binds to MAO without metabolization.[22] On the other hand, imipramine is an inhibitor of the amine pump on the nerve ending of synapses and it inhibits ^{123}I-IMP adsorption to the alveolar macrophages. Therefore it is possible that high adsorption of I-123 IMP to the alveolar cells is related to MFO, MAO or the amine pump.

Up to now there has been no established clinical study of amine movement and the metabolism function of the human lung. We think the analysis of ^{123}I-IMP movement in the lung could become a new method for studying nonrespiratory lung function and lung disease.

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