Deposition and clearance of inhaled ^{18}FDG powder in patients with chronic obstructive pulmonary disease

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Deposition and clearance of inhaled ^{18}FDG powder in patients with chronic obstructive pulmonary disease. M. Yanai, J. Hatazawa, F. Ojima, H. Sasaki, M. Itoh, T. Ido. ©ERS Journals Ltd 1998.

ABSTRACT: As freon is limited in its use as a generator for aerosol inhalation, powder particles are used as an alternative for inhalation therapy.

The pulmonary deposition and clearance of inhaled powder particles was studied by positron emission tomography (PET) in ten patients with chronic obstructive pulmonary disease (COPD) and in five normal controls. The powder, 5 μm in mean diameter, was water soluble and labelled with 2-deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}FDG). Powder inhalation was done with single deep inspiration from residual volume to total lung capacity.

The initial deposition ratio in the right or left lung field to total inhaled dose, measured by an anteroposterior rectilinear scan, did not differ between normals and COPD patients. Ratios of radioactivity detected within the central and peripheral regions (the central to peripheral ratio) measured by the PET scan was not significantly different between COPD patients (4.8±2.6, mean±SD) and normals (2.6±0.8, mean±SD). However, the regional powder deposition in peripheral lung fields measured by the PET scan was significantly more uneven in COPD patients than in normal lungs. The clearance rate of ^{18}FDG, defined as the retention ratio of ^{18}FDG activity to the initially deposited ^{18}FDG at 60 and 120 min after inhalation, in the trachea, large bronchi or peripheral lung fields measured by tomographic scan showed a wider variation in COPD patients than in normals.

To conclude, inhaled powder tended to be deposited more centrally and was distributed more unevenly in the peripheral lung in chronic obstructive pulmonary disease patients than in normals. This could be a limitation of powder inhalation used for therapy in chronic obstructive pulmonary disease patients.
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Although aerosols have been widely used therapeutically to treat diseased lungs, aerosols generated with freon are in limited use in clinical therapy because of air pollution caused by freon. The inhalation of powder particles has been introduced as an alternative inhalation method. However, little is known about the characteristics of powder inhaled in the diseased lungs. In a previous study [1], it was observed that the initial deposition in the lung fields was approximately half of the total powder inhaled in normal volunteers, although a relatively high deposition was observed proximally. In addition, the deposited radioactivity gradually decreased, along with tracheobronchial mucociliary clearance and with alveolar and bronchial epithelial permeability [1].

Aerosols have been used therapeutically to treat diseased lungs and the deposition of inhaled radioparticles in the lung has been studied by gamma camera in normal subjects with or without bronchoconstriction [2], and in patients with chronic obstructive pulmonary disease (COPD) [3, 4] or bronchial asthma [5, 6]. The distribution in the central and peripheral lung zones between control and narrowed airways is not consistent. Previous reports could not determine whether the regional distribution of inhaled

particles is even in peripheral lung fields, because of the limited performance of the detection system [1]. However, the evaluation of the distribution in the lung of the radioaerosols was carried out by nontomographic imaging, exposing these studies to a number of criticisms. Spatial resolution deteriorates with depth, and an indeterminate degree of signal attenuation occurs owing to tissue absorption of the emitted photons and noise arising from scattered photons. Furthermore, because of the two-dimensional character of the detection system, there is a superimposition of signal with depth, which results in the subsequent degradation of spatial resolution [7].

Positron emission tomography (PET) largely overcomes these shortcomings by employing the coincidence detection of annihilation photons [8]. The geometry of the coincidence detection system provides uniform sensitivity and resolution, and the effect of photon attenuation can be accurately measured by a transmission scan. In the present study, using PET, the regional deposition and clearance of an inhaled, water-soluble powder labelled with 2-deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}FDG) was investigated after a deep inspiration manoeuvre in COPD.

Methods

Subjects

Five normal subjects and 10 patients with COPD were studied. Normal subjects were the same as in a previous study [1]. All subjects with COPD fulfilled the criteria of the American Thoracic Society for the diagnosis of COPD [9]. The physical and pulmonary function data of normals and COPD patients are listed in table 1. None of the subjects had bullous disease, and this was confirmed by computed tomography (CT) scan.

The present clinical PET study was approved by the Tohoku University Ethics Committee. Informed consent was taken from all of the candidates.

Radiopharmaceutical preparations

Fine powder containing 18FDG was prepared [10]. 18FDG powder was administered by means of a Rotahaler (Glaxo, Research Triangle Park, NC, USA). The synthesis of the 18FDG powder has been described elsewhere [11]. In brief, diethyl ether was dropped into a methanol solution of 18FDG and 20 mg of sugars (glucose, lactose and 10 mg of N-acetyl neuraminate) with ultrasonication (200 W, 39 kHz). Methanol in the crystals was eliminated by washing twice with diethyl ether and the crystals were mixed with lactose as an additive and dried in a vacuum. Then, 40 mg of the powder was put into hard gelatin capsules for the inhalation experiment. The 18FDG powder is a heterodisperse aerosol with a mean geometric particle size of 5 ± 1 μm, estimated by measurements from light microscopy. The radioactivity of 18FDG prepared in the capsule ranged from 56–74 MBq at inhalation. The quantity of 18FDG powder including sodium-N-acetyl-neuraminate as a seed crystal was <4 mg.

Inhalation manoeuvres

The inhalation was carried out in a sitting position with a single deep inspiration from residual volume to total lung capacity without added external resistance, followed by 5 s of breath-holding. The powder was dispersed into the inhaled airstream by the subject's inspiratory effort. None of the subjects coughed during the procedure. Prior to the study, all subjects repeatedly practised the manoeuvre and timing of inhalation so as to inspire at a rate of approximately 60 L·min⁻¹ with a dummy inhaler con-nected to a spirometer. No one failed to inhale the 18FDG powder. The mean inspiratory flow rates were 66 ± 7 L·min⁻¹ (mean±SD) for normal and 55 ± 11 L·min⁻¹ (mean± SD) for COPD patients. The inspiratory flow rate was not significantly different between the two groups. Subjects rinsed their mouth with water to remove radioactivity in the oral cavity immediately after inhalation. The total inhaled 18FDG was calculated by subtracting the residual 18FDG in the inhaler and the 18FDG activity in the water after rinsing.

Scanning procedures

Subjects were studied with a single ring scanner, ECAT II (EG&G, Ortec, TN, USA). The spatial resolution of the image was 15 mm and slice thickness was 18 mm at full width of half-maximum (FWHM).

Two tomographic scans, one 2–3 cm above the carina and the other 10 cm below this scan, were performed just after inhalation, and 60 and 120 min thereafter. The data acquisition rate was 5 min·plane⁻¹. Rectilinear scanning from the oral cavity to the upper abdomen, which took 5 min, followed the tomographic scanning.

Prior to the 18FDG inhalation, the regional pulmonary blood volume was measured by the PET as follows [12]. 11C-Carbon monoxide (11CO) was inhaled until a count rate of 4,000 counts per second (cps) in the tomographic plane was obtained. Scans of the upper and lower levels were performed, respectively, after an equilibrium period of 5 min. Venous blood was taken during the scanning to measure whole blood 11CO activity.

Images of 18FDG and 11CO were corrected for attenuation by a transmission scan obtained by an external ring source of 68Ge.

Distribution of inhaled 18FDG powder

The initial deposition in the body was evaluated by the rectilinear image obtained 10 min after inhalation. Regions of interest (ROI) for the oral cavity, right and left lung fields, the mediastinum and the upper digestive tract were determined. The radioactivity ratio (%) of each ROI to total image counts was calculated.

To evaluate the regional distribution of initial deposition in the peripheral lung fields, the lung fields of the lower tomographic scans were partitioned into eight parts (fig. 1a). Right and left lung fields, the borders of which

Table 1. – Physical characteristics and pulmonary function tests in normal subjects and patients with chronic obstructive pulmonary disease (COPD)

	Age yrs	Sex M/F	Height cm	Weight kg	VC L	FEV1 % pred	TLC % pred	FRC % pred	$D_{L,CO}$ % pred	C_{st} L·cmH$_2$O⁻¹	P_{a,O_2} mmHg	P_{a,CO_2} mmHg
Normal (n=5)												
mean	46	5/0	163	57	101	103	ND	ND	ND	ND	83	39
(SD)	(6)		(5)	(6)	(10)	(14)					(10)	(3)
COPD (n=10)												
mean	70**	8/2	157	49*	102	61**	117	124	86	0.37	74	40
(SD)	(5)		(6)	(5)	(16)	(16)	(10)	(20)	(10)	(0.12)	(10)	(3)

VC: vital capacity; FEV1: forced expiratory volume in one second; TLC: total lung capacity; FRC: functional residual capacity; $D_{L,CO}$: pulmonary diffusing capacity for carbon monoxide; C_{st}: static pulmonary compliance; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; M: male; F: female. Significant differences are reported as *: $p<0.05$; **: $p<0.01$, compared with normal subjects. ND: not determined. 1 mmHg=0.133 kPa.

were determined from the transmission scan at the same scanning level, were each divided into four radial parts. Assuming that the peripheral lung field was a half-ring, each radial part was partitioned to have the same angle (45°) from the centre of the half-ring. An outer borderline of each ROI was drawn 1.5 cm inside the lung border or the mediastinum to take into consideration the spatial resolution of the scanner. The inner borderline of each ROI was drawn 1.5 cm within the outer ROI. The mean radioactivity of each ROI was measured and the coefficient of variation of eight ROI in normals and COPD patients was calculated. To assess the central to peripheral (CP) ratio by the PET scan, ROI were defined by the technique of PHIPPS et al. [13] with some modifications to represent central and peripheral lung deposition. Because the slice thickness adopted (18 mm at FWHM) was thin enough to avoid possible interference by activity present within the stomach, both right and left lungs were studied. The ROI, the borders of which were determined from the transmission scan at the same scanning level, were in the transverse plane (fig. 1b).

Measurement of tracheobronchial clearance

In the tomographic images, circular ROI were set in the trachea on the upper image and in the basal bronchus or intermediate trunk on the lower image. The ratio of resid-
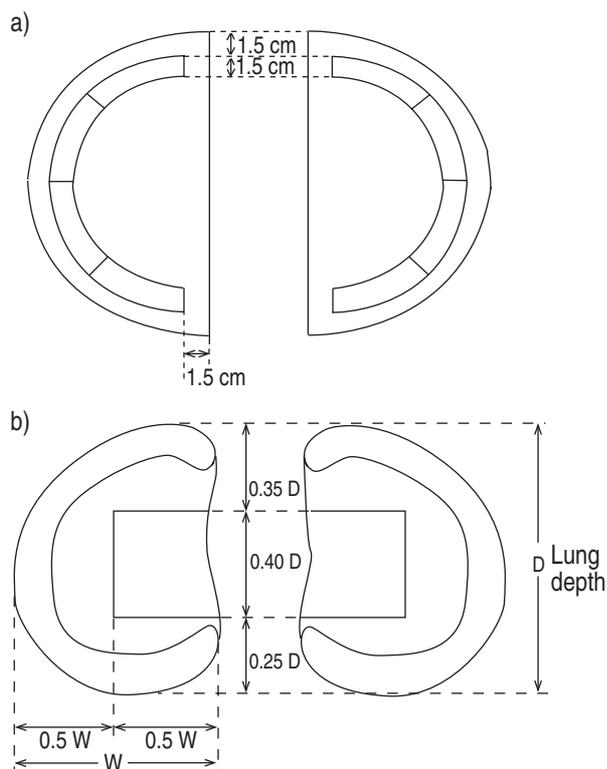

Fig. 1. – Partitioning of lung fields of tomographic scans. a) Assuming that the peripheral lung field was a half-ring, each radial part was partitioned to have the same angle (45°) from the centre of the half-ring. The outer borderline of each region of interest was drawn 1.5 cm inside the lung border or the mediastinum to eliminate the partial volume effect. b) The central and peripheral regions of interest defined in the lower tomographic scan of the positron emission tomographic image in the right and left lung.

ual [18]FDG activity at 60 and 120 min to the activity at the initial deposition was determined as a retention ratio (%) of [18]FDG for the trachea or right and left large bronchus.

Measurement of lung field clearance

The ROI in the lung field was determined on the lower tomographic images. The borderlines of lung fields were determined from the transmission scan at the same level. The outer lines of the half-ring-like ROI were set 1.5 cm inside the borderline and 1.5 cm apart from the mediastinum. The inner lines of the ROI were drawn 1.5 cm within the outer line. The regional pulmonary blood volume was obtained by taking the ratio of lung pixel counts for [11]CO to whole blood counts measured with a cross-calibrated well counter. The intravascular [18]FDG activity in these ROI, calculated from a pulmonary blood pool image and whole blood [18]FDG activity, was subtracted [1]. The lung field retention ratio of [18]FDG was determined in the same way as the tracheobronchial retention ratio described above.

Measurement of blood volume and extravascular lung density

The regional pulmonary blood volume (PBV; mL·mL^{-1} thoracic volume) was obtained by taking the ratio of lung pixel counts for [11]CO to whole blood counts measured with a cross-calibrated well counter. To correct the difference between pulmonary and large-vessel haematocrit, the value of 0.9 was used [14].

The transmission image for tissue attenuation correction for lung density (LD) measurement was used [14]. Pixel counts for external [68]Ge were linearly related to physical density. By taking the ratio of lung pixel counts to heart pixel counts, LD (g·mL^{-1} thoracic volume) was calculated. Extravascular LD (ELD; g·mL^{-1} thoracic volume) was then obtained as LD minus PBV.

Absorption of [18]FDG into the blood

Because [18]FDG is a water-soluble material and metabolic substance, clearance through the bronchopulmonary mucosa as well as the mucosa of the oral cavity or digestive tract is anticipated. To evaluate the amount of [18]FDG transported to the circulation, venous blood was taken at 15, 20, 60, 90 and 120 min after inhalation. Whole blood radioactivity was measured using a cross-calibrated well counter.

Statistics

Statistical analysis was carried out with the Student's t-test, and significance was accepted at p-values <0.05. Data are reported as mean±SD.

Results

The initial distribution of inhaled [18]FDG powder by rectilinear imaging in the oral cavity, the mediastinum, left and right lung, and the upper digestive tract is summarized

Table 2. – Radioactivity ratio (%) of organs to total 2-deoxy-2-[18F]-fluoro-D-glucose count in a rectilinear image just after inhalation

	Right lung	Left lung	Oral cavity	Media.	Stom.	Both lung fields
Normal (n=5)						
mean	24	24	29	10	12	48
(SD)	(6)	(5)	(13)	(8)	(15)	(10)
COPD (n=10)						
mean	21	18	29	16	16	39
(SD)	(6)	(6)	(9)	(7)	(13)	(12)

Media.: Mediastinum; Stom.: Stomach; COPD: chronic obstructive pulmonary disease.
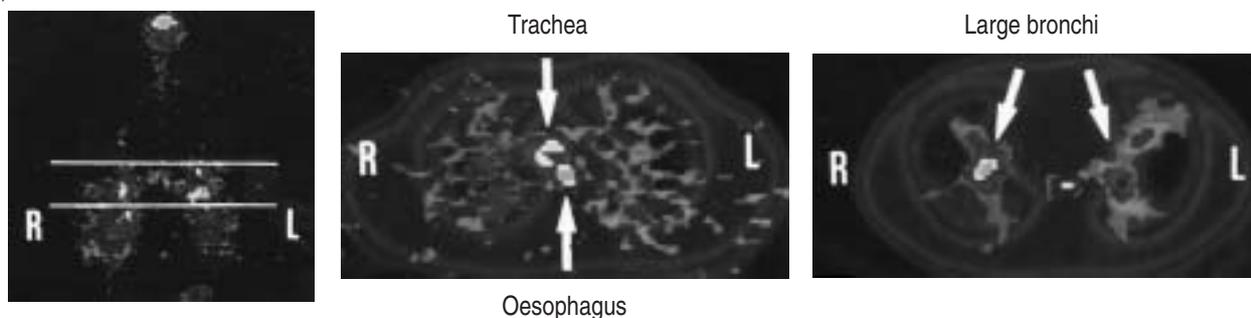
in table 2. The inhaled 18F dose was 19.5±6.8 MBq in normals and 18.7±7.2 MBq in COPD patients, which were not significantly different. There was no significant difference in the 18FDG deposition to corresponding ROI between normals and COPD patients.

Figure 2 represents a rectilinear image and tomographic images of COPD patients after inhalation. The images of the transmission scan at the same scanning level are superimposed on the PET scans. In the upper PET scans just after inhalation (middle row, top panel), the deposition to the trachea is clearly distinguished from that of the oesophagus.

The CP ratios measured by the lower PET scan in normals and COPD patients are shown in fig. 3. Although significance was not reached (p=0.08), the CP ratio tended to be higher in the COPD group (4.8±2.6) than in normals (2.6±0.8), suggesting that powder was deposited more centrally in COPD subjects.

Figure 4 shows the coefficient of variation of the initial 18FDG deposition in eight divided lung fields on the lower tomographic scans for normals and COPD pati-

ents. It was significantly greater in COPD patients (1.01±0.46) than in normals (0.26±0.12) (p<0.01), indicating that the distribution of particles in the lung fields after deep inspiration is more uneven in COPD patients than in normals.

Figure 5 shows 18FDG retention ratios at the trachea, and right and left large bronchi at 60 and 120 min after inhalation. There was no significant difference in retention ratio for the trachea, and right and left large bronchi at 60 and 120 min between normals and COPD patients. Increases in the retention ratio were observed at 60 min in some bronchi with COPD patients.

Mean lung field retention ratios corrected with intravascular 18FDG at 60 and 120 min are shown in fig. 6. No significant difference was observed in the retention ratio

Fig. 3. – Central to peripheral (CP) ratios on the tomographic scans in normals (N) and patients with chronic obstructive pulmonary disease (COPD). Bars represent mean±SD. NS: nonsignificant difference between groups.
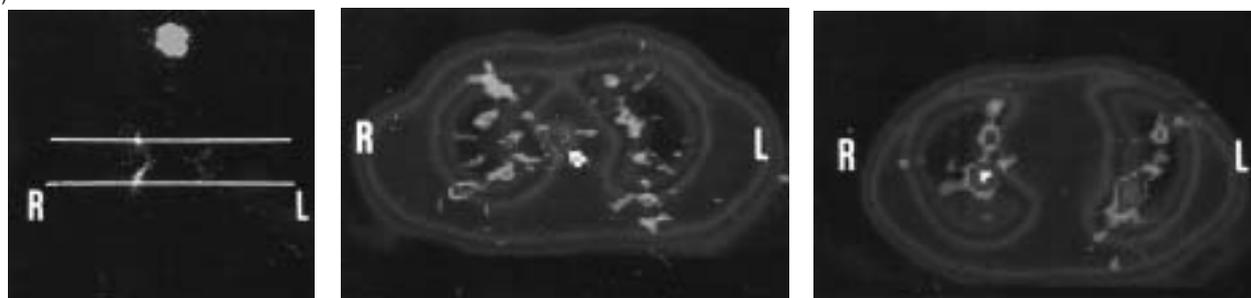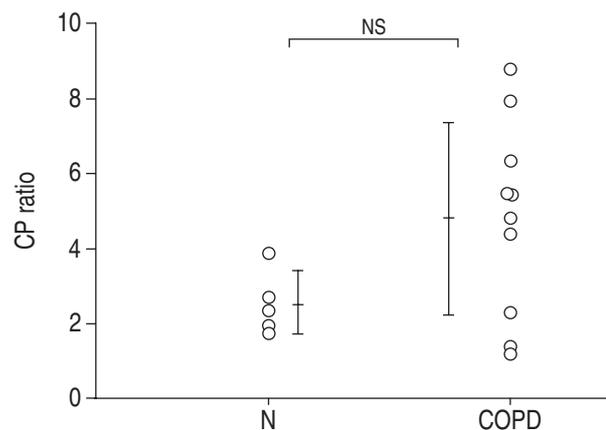
a)

Oesophagus

b)

Fig. 2. – Rectilinear images (left column) and tomographic images of 18FDG powder at 2–3 cm above the carina (middle column) and 10 cm below the scan (right column) in patients with chronic obstructive pulmonary disease a) just after and b) 1 h after powder inhalation. The two lines in the rectilinear images indicate the level of tomographic scanning. R and L indicate the right and left sides of the patients. The images of the transmission scan at the same scanning level are superimposed on the tomographic images.
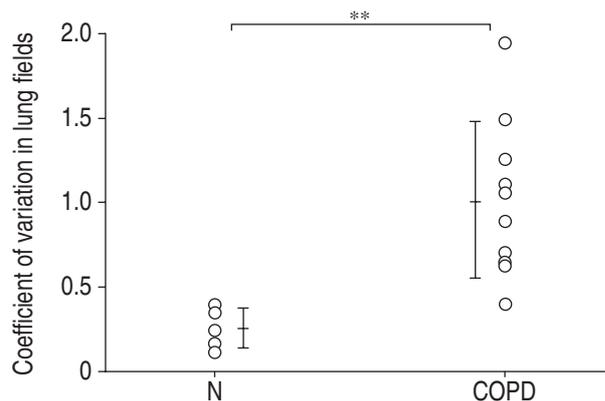
Fig. 4. – Coefficient of variation in eight lung fields on the lower tomographic scans in normals (N) and patients with chronic obstructive pulmonary disease (COPD). Right and left lung fields, the border of which was determined from the transmission scan at the same scanning level, were each divided into four radial parts. Bars represent mean±SD. **: significant difference between groups, p<0.01.

between normals and COPD patients in the left lung; however, for the right lung at 60 min it was significantly lower in COPD patients than in normals (p<0.05).

In the peripheral alveolar area, mean LD, PBV and ELD in normals and patients with COPD are summarized in table 3. There is no significant difference in LD, PBV or ELD between normals and patients with COPD.

Figure 7 shows venous blood radioactivity after ^{18}FDG powder inhalation curing the PET measurement. It increased gradually during the first 60 min and reached the steady state thereafter in normals and COPD patients. Although some COPD patients showed a higher level than normals there was no significant difference in venous blood radioactivity at any time point between normals and COPD patients.

Discussion

The present study showed that inhaled powder does not distribute uniformly to the lung fields on the horizontal tomographic plane after deep inspiration in patients with COPD. Because no bullous lesion was found in any COPD patients, this uneven deposition would be due to regional uneven distribution of airway narrowing or com-
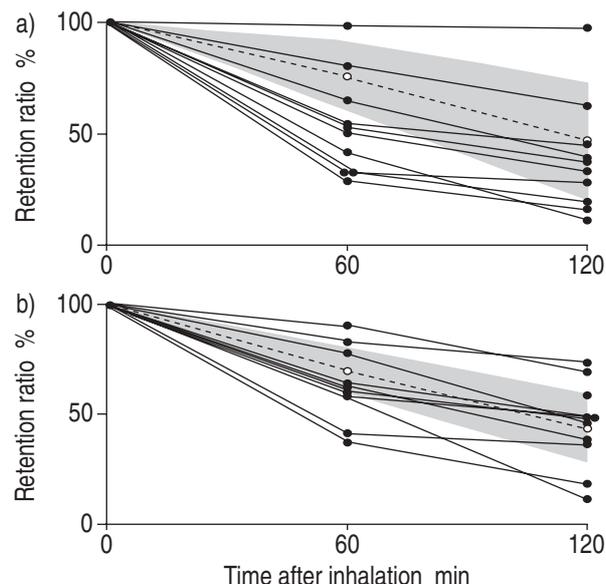

Fig. 6. – Retention ratio of 2-deoxy-2-[^{18}F]-fluoro-D-glucose at 60 and 120 min after inhalation in a) right and b) the left lung in patients with chronic obstructive pulmonary disease. Data of normals are shown as mean (○) ±SD range (shaded).

Table 3. – Mean lung density (LD), pulmonary blood volume (PBV) and extravascular lung density (ELD) in the alveolar area

	LD g·mL^{-1} TV	PBV mL·mL^{-1} TV	ELD g·mL^{-1} TV
Normal (n=5)			
mean	0.27	0.14	0.13
(SD)	(0.03)	(0.03)	(0.03)
COPD (n=10)			
mean	0.24	0.12	0.12
(SD)	(0.05)	(0.03)	(0.03)

COPD: chronic obstructive pulmonary disease; TV: thoracic volume.

pliance. In this study, deep inspiration from residual volume to total lung capacity, which makes the turbulent flow dominant towards the periphery, was employed. However, we believe that the regions we measured were peripheral enough to assume that the flow there was almost laminar. Therefore, the sparse radioactive region, corresponding to
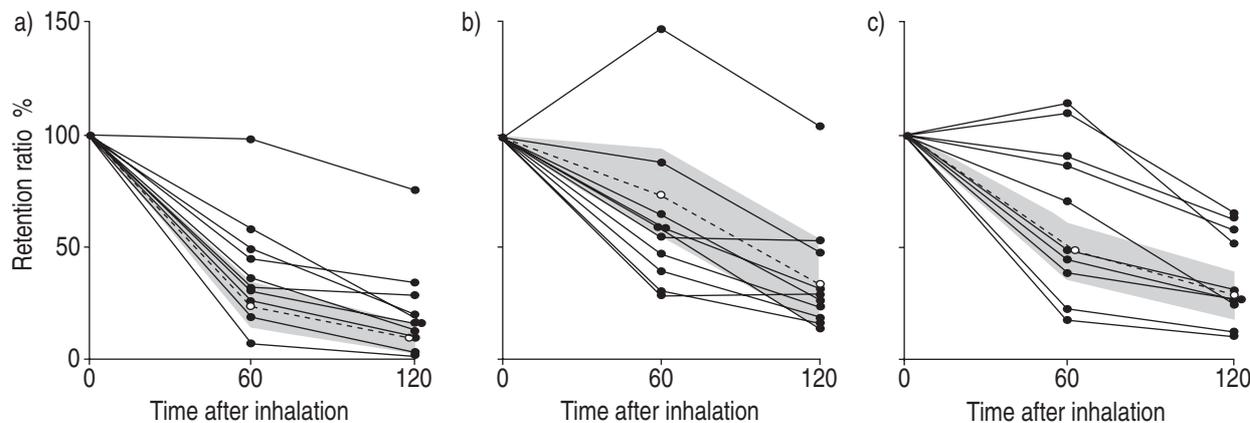

Fig. 5. – Retention ratio of 2-deoxy-2-[^{18}F]-fluoro-D-glucose at 60 and 120 min after inhalation at a) the trachea, b) right large bronchus and c) left large bronchus to initial deposition in patients with chronic obstructive pulmonary disease. Data of normals are shown as mean (○) ±SD range (shaded).
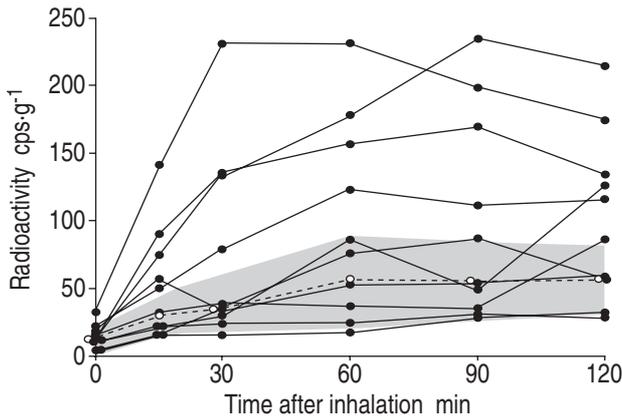
Fig. 7. – Whole blood 2-deoxy-2-[18F]-fluoro-D-glucose (18FDG) activity plotted against sampling time in patients with chronic obstructive pulmonary disease. 18FDG activity is corrected for an inhaled dose of 37 MBq. Data of normals are shown as mean (○) ±SD range (shaded). cps: counts per second.

reduced airflow, may result from airway obstruction or air trapping. In this study, the deposition ratio of radioactive powder in the lung field to the total inhaled dose on the rectilinear scan was not significantly different between normals and COPD patients. Besides, the CP ratio measured by the PET scan did not significantly differ between normals and COPD patients, although particles tended to be deposited more centrally in COPD patients. Therefore, even if deep inspiration would penetrate the powder to the total lung in COPD patients as well as in normals, uneven distribution of particles in the peripheral lung indicates that inhaled particles may show limited deposition in the obstructive lung fields.

In this study, the normal and COPD groups were not quite matched regarding age and number. Age differences between normal and COPD subjects might have exaggerated uneven deposition of particles in the COPD group. Small variations in the deposition pattern, retention ratio and 18F blood activity among normal subjects might excuse the small numbers in the group.

Each PET scan took 5 min and the rectilinear scan also took 5 min. Therefore, significant clearance may have occurred before the scanning was complete, and it may make the result of initial deposition difficult to interpret, especially for the rectilinear scan. However, it may similarly affect the deposition in the lung field between normals and COPD subjects, because the clearance ratio in the trachea, large bronchi and peripheral lung fields did not significantly differ between the two groups, except for the right peripheral lung field at 60 min after inhalation.

It has been reported that the aerosol deposition within the lung in patients with COPD observed in a rectilinear scan is decreased compared with normal subjects [3, 4]. In these studies, subjects inhaled aerosol with tidal breathing [4] or a limited inspiratory volume of <1 L [3]. In the present study, subjects inhaled powder from residual volume to total lung capacity. RYAN et al. [15] reported that aerosols deposit more peripherally during tidal breathing than with a single deep breath. There have been reports that once the aerosol has entered the lungs, deposition by impaction in large bronchi is more likely in patients with COPD, whose airways may be narrowed by a combination of bronchospasm, oedema and mucous hypersecre-

tion [3, 4, 7], and that the penetration of particles is inversely related to flow rate during inspiration [3]. In the present study, inspiratory flow rate during inhalation tended to be lower in COPD patients than in normals. This may imply that the deposition of inhaled powder in the central airway could have been underestimated in COPD patients, resulting in a reduced value for the CP ratio in the COPD group and making it not significantly different from the normal group.

A water-soluble powder was used to measure the deposition and clearance in the lung. In assessing clearance from the lung, two different routes exist; one by mucociliary transport along the tracheobronchial tree and the other by transepithelial absorption into the blood or lymphatics [16–18]. Because of this feature, the lung retention ratio depends mainly on the permeability in the peripheral lung, where the mucociliary transport takes place very slowly [19]. Previous reports have demonstrated that airway permeability is increased in unstable asthmatics [20] and COPD patients [21], but not in stable asthmatics [22]. In the present study, the retention ratio of the right peripheral lung at 60 min after inhalation was significantly lower in COPD patients than in normals, suggesting that the epithelial permeability of the small airways and alveoli may be increased in COPD subjects.

There are wide variations in the retention ratios at the trachea and large bronchi in COPD patients. In some bronchi at 60 min, the retention ratio increased compared with the initial deposition. This phenomenon implies that mucociliary transport was regionally impaired down to proximal sites from the bronchus. It suggests that, in COPD patients, mucociliary dysfunction could take place regionally, resulting in an accumulation of sputum which would be difficult to remove without the help of a mechanical force, such as cough, at these lesions.

PET measurement provides regional changes of pulmonary blood volume and extravascular lung density in various diseases. In patients with congestive heart failure, pulmonary oedema was detected as an increase in extravascular lung density [23]. In patients with interstitial lung disease, the reduction in blood volume was well correlated with the severity of pulmonary fibrosis [12]. In the present study, the patients with COPD did not show any significant difference in blood volume and extravascular lung density. Since the primary target organ is the airway, it is important to measure the blood volume in the airway. However, because of the low radioactivity of 11CO in the blood as well as low blood perfusion in the bronchial circulation, 11CO activity in the airway could not be discriminated from the background. Therefore, the regional blood volume in the airway was not examined.

There was no systemic correlation between blood radioactivity and the initial deposition pattern on the rectilinear scan, and the regional deposition in the peripheral lung, CP ratio, retention ratio in the trachea, large bronchi and peripheral lung on tomographic scan and pulmonary function tests.

Powder inhalation devices for β2-agonists have been demonstrated to be useful in patients with bronchial asthma [24]. A comparison of β2-agonist powder and aerosols in chronic obstructive pulmonary disease revealed that both provide bronchodilatation equally [25]. The pulmonary regional distribution of aerosols has been studied using planar and single photon emission computed tomography

in normal subjects [26]. The present study investigated the deposition and clearance of inhaled powder particles in chronic obstructive pulmonary disease by positron emission tomography using 2-deoxy-2-[^{18}F]-fluoro-D-glucose powder. We conclude that inhaled powder tends to be deposited more centrally and is significantly unevenly distributed in the peripheral lung in chronic obstructive pulmonary disease patients compared with normals. This could be a limitation of powder inhalation utilized for therapy in chronic obstructive pulmonary disease patients.

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