Uptake of ^{18}fluorodeoxyglucose in the cystic fibrosis lung: a measure of lung inflammation?

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ABSTRACT: Positron emission tomography is a three-dimensional imaging technique that measures physiological effects, including metabolism. ^{18}Fluorodeoxyglucose has been extensively used as a tracer of cellular energy metabolism in the brain and in tumour detection. As neutrophils utilise glucose as an energy source during their respiratory burst, it was hypothesised that ^{18}fluorodeoxyglucose uptake, by these cells, could be interpreted as a measure of neutrophil activation in cystic fibrosis (CF).

Ten adult CF patients were given a bolus intravenous injection of ^{18}fluorodeoxyglucose, followed by a 90-min dynamic mid-lung acquisition scan. Right-lung ^{18}fluorodeoxyglucose uptake was assessed using a Patlak plot and values were converted to glucose utilisation. Three clinically inactive pulmonary sarcoidosis patients served as controls.

From the 10 CF patients with baseline sputum neutrophils of 14×10^6 cells·mL^{-1} who were investigated, seven were found to have sputum at a normal or slightly depressed glucose utilisation rate (mean 1.33 µmol·g^{-1}·h^{-1}) compared with a mean of 2.82 µmol·g^{-1}·h^{-1} for the sarcoidosis patients. In eight patients, receiving inhaled tobramycin therapy, no change in lung glucose utilisation or sputum neutrophil counts were found.

Despite high-sputum neutrophil levels, lung glucose utilisation was not elevated in patients with cystic fibrosis.
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Positron emission tomography (PET) is a powerful, quantitative, nuclear medicine tomographic imaging technique. PET can be used to measure physiological effects such as blood flow, metabolism, ventilation, receptor occupancy, regional dose delivery and pharmacokinetics of radiolabelled drugs [1]. It combines principles of image reconstruction from projections with the use of specific biological molecules labelled with positron-emitting radioisotopes (^{11}C, ^{18}F, ^{15}O, ^{13}N) allowing regional measurements of dynamic processes to be taken.

^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}FDG) is a tracer of cellular energy metabolism. It has been used extensively to monitor the metabolic activity of cells *in vivo* in the brain [2–5] and to detect tumours [6–8]. ^{18}FDG differs from glucose by the substitution of the hydroxyl group with a fluorine atom on the second carbon of the glucose. When injected intravenously, ^{18}FDG rapidly diffuses into the extracellular spaces throughout the body. It is transported into living cells by the same mechanism as glucose, *via* the D-glucose transporter and is phosphorylated by hexokinase to fluoro-deoxyglucose-6-phosphate. The deoxy substitution at the second carbon position prevents further metabolism and the product accumulates in the cell at a rate that reflects glucose metabolism. Increased glucose consumption is assumed to lead to an increased rate of tracer uptake. The rate of accumulation of ^{18}FDG in tissue after intravenous injection reflects the combined transport and hexokinase activity in the cells [9]. ^{18}FDG-PET studies of the lung are still relatively few compared with the number of oncological, neurological and cardiac studies.

The inflammatory process, in particular neutrophils, has been implicated in the pathogenesis of a variety of lung diseases including cystic fibrosis (CF), bronchiectasis, and chronic bronchitis. Neutrophils contribute to pulmonary destruction by production and release of cytotoxic enzymes (*e.g.* elastase, myeloperoxidase) and toxic oxygen metabolites [10]. Markers of inflammation in blood, bronchoalveolar lavage (BAL), sputum and lung biopsy serve as indirect measurements of inflammation, making the detection of regional variation of inflammation in the lung impossible [11–14]. ^{18}FDG uptake is a well-validated *in vivo* measure of tissue glucose metabolism using PET. ^{18}FDG preferentially accumulates in areas with increased metabolism, such as tumours, in which the rate of uptake is six to seven times higher than normal tissue [7], and sites of infection where the metabolic rate of glucose is elevated in activated inflammatory cells, such as neutrophils [15–17]. It is hypothesised that ^{18}FDG and PET could be used to measure and monitor the metabolic activity of neutrophils in neutrophil-dominated inflammatory diseases of the lung including CF. An increase in the ^{18}FDG signal is detected in the presence of neutrophils, lymphocytes and macrophages. These cells have a high anaerobic to aerobic metabolic ratio due to a relative lack of oxidative enzymes. Compared with aerobic glucose degradation, anaerobic metabolism consumes considerably more glucose to produce equivalent amounts of adenosine triphosphate [9]. Uptake of ^{18}FDG reflects glucose metabolism, therefore, its uptake is accelerated in anaerobic glycolysis. Neutrophils utilise glucose as the main source of energy, deriving most of their energy supply from glycolysis [15, 18]. Glucose utilisation in neutrophils

is 10-times higher than that in lymphocytes [16]. Although macrophages can use glycolysis, during phagocytosis, they rely more on oxidative phosphorylation in well-oxygenated areas such as the lungs [18]. While the use of [18]FDG-PET in detecting and monitoring inflammatory events in the lung is relatively new, studies have shown that an increase in [18]FDG uptake indicates the presence of inflammatory activity, particularly neutrophil activation. In patients with acute lobar pneumonia, microautoradiography of ^{18}F in lavage fluid showed radioactivity localised to >90% of the neutrophils [19]. In an *in vivo* animal study using a rabbit model of acute (Streptococcal pneumonia) and chronic (bleomycin-induced injury) lung inflammation and autoradiography, JONES *et al.* [20] showed that [18]FDG uptake was localised to neutrophils and not macrophages, which outnumbered neutrophils 5:1 in the case of bleomycin-induced lung injury.

Progressive respiratory disease is associated with significant morbidity and mortality in CF patients and is the leading cause for 80% of deaths each year [21], with the chronic neutrophil-dominated inflammatory process firmly implicated in the destruction of the lung in CF [22]. Therefore, it is possible that the [18]FDG-PET technique could be used to study the degree of lung inflammation, the progression of disease and to assess local tissue response to anti-inflammatory therapeutic interventions. The objectives of this study were as follows: 1) to determine the extent of inflammation in the lungs of patients with CF using [18]FDG and PET imaging; 2) to ascertain if a correlation could be demonstrated between the degree of lung neutrophilia, as measured by the accumulation of [18]FDG in the lung, with the neutrophil values obtained from sputum cytology; and 3) to determine if [18]FDG and PET could detect changes in the degree of lung inflammation after a 28-day inhaled tobramycin treatment.

Methods

Subjects

Patients with CF, who were ⩾16 yrs, chronically infected with *Pseudomonas aeruginosa* and in a stable clinical condition (defined as no acute exacerbations in the previous 4 weeks) were enrolled in the study. Subjects with nonactive sarcoidosis served as controls. The study was approved by the Hamilton Health Sciences Research Ethics Committee and written informed consent was obtained before the initiation of the study.

Study design

The study consisted of two PET scans of the lung, separated by 28 days of nebulised tobramycin therapy. Patients nebulised 160 mg of tobramycin (Eli Lilly, Scarborough, Canada) *b.i.d.* using a Pari LC Star nebuliser and ProNeb Turbo compressor (PARI Respiratory Equipment, Inc., Mississauga, Canada).

A spontaneously expectorated sputum specimen was obtained prior to each PET procedure. Sputum cytology was performed as described by PIZZICHINI *et al.* [23] with modifications for CF [24]. Spirometry was measured at the beginning and end of each PET scan, according to American Thoracic Society standards [25].

[18]F-2-fluoro-2-deoxy-D-glucose and positron emission tomography methods

Patients were given a bolus intravenous injection of 1.0–1.5 mCi of [18]FDG (50 µCi·kg body weight[-1]) into a vein in the hand or arm, while in the supine position on the scanner bed of the ECAT ART scanner (CPS Innovations, Knoxville, TN, USA) [26]. A 90-min dynamic acquisition (18 frames, 5 mins per frame) was obtained over the mid-sternum region of the lung, followed by a 10 min acquisition at three bed positions: mid-sternum and sections immediately above and below. Using an external source of ^{137}Cs, a transmission scan to correct for tissue attenuation was obtained at the end of imaging with the patient in the same supine position.

A region of interest (ROI) was drawn on the mid-transaxial slice, defining the right lung on the transmission scan. This ROI was then transferred to the emission scan, where the mean radioactivity in the area was calculated at 12 time points (over 0–60 mins, at 5-min intervals) for all slices. A simple, noninvasive method, previously validated in the Department of Nuclear Medicine, McMaster University, ON, Canada, was used to determine plasma activity [27, 28]. The plasma ^{18}F levels were estimated by drawing an ROI around a vein in the shoulder region. As, [18]FDG equilibrates instantaneously between the plasma and red blood cells, the distribution ratio is close to unity and the time-activity curves in whole blood and plasma are identical [28]. Time activity-curves were constructed using these data.

The cumulative rate of [18]FDG uptake in the extravascular tissue was calculated using all transaxial slices within the right lung. The serial measurements of the ratio of regional accumulation of ^{18}F in the lung fields, compared with plasma ^{18}F concentrations over the 90-min dynamic scan time, were used in a graphical analysis [29]. The serial measurements of the ratio of regional lung tissue to plasma ^{18}F concentration (normalised activity) were drawn in a Patlak plot against the ratio of cumulative to instantaneous plasma ^{18}F over the 90-min period after the intravenous [18]FDG infusion (normalised time) [29]. The slope of this line is equal to the rate constant (ki) for the metabolic trapping of FDG in the lungs (mL·g^{-1}·h^{-1}); ki is converted to glucose utilisation (µmol·g^{-1}·h^{-1}) by multiplying it by the mean plasma concentration of stable glucose (representative value of 4.6 µmol·mL^{-1}) [18].

Data analysis

The rate of accumulation of [18]FDG was plotted and the ki were compared pre- and postantibiotic therapy for each subject using the paired t-test. All statistical tests were two-sided and significance was accepted at the level of 95%. Sputum neutrophil counts are not normally distributed and were therefore expressed as median and interquartile range (IQR) and compared pre- and postantibiotic therapy using the nonparametric Wilcoxon signed-rank test. The correlation between the [18]FDG uptake and neutrophil counts was calculated using Spearman's correlation coefficient (r_s).

Results

The characteristics of the 10 CF patients and three control (clinically inactive sarcoidosis) subjects are presented in table 1. Two CF patients had diabetes mellitus. In patients with diabetes, it has been shown that administration of [18]FDG does not adversely affect their insulin therapy and neither does [18]FDG uptake [30]. A total of four CF patients were receiving inhaled steroid therapy, although no patients were prescribed recombinant human deoxyribonuclease treatment. From the 10 CF patients enlisted, two did not complete the study; one withdrew after their first visit and one had an acute exacerbation secondary to a respiratory infection.

Representative images for one transaxial tomographic slice

Table 1. – Cystic fibrosis (CF) and control (sarcoidois) subject characteristics

Characteristics	CF	Sarcoidosis
Subjects	10	3
Male	5	1
Female	5	2
Age yrs	24.7±5.4	55.7±11.0
FEV1 L	2.06±0.8	2.45±0.88
FEV1 % pred	53.5±19.4	85.0±9.0
Disease status		
Mild FEV1 >60%	5	3
Moderate FEV1 40–60%	2	0
Severe FEV1 <40%	3	0
CFTR Genotypes		
ΔF508 homozygotes	3	
ΔF508 heterozygotes	4	
Other	2	
Unknown	1	

Data are presented as n or mean±SD unless otherwise stated. FEV1: forced expiratory volume in one second; % pred: % predicted; CFTR: cystic fibrosis transmembrane conductance regulator.

in the thorax region of a CF patient are shown in figure 1. Corresponding activity curves in the blood and the right lung are shown in figure 2. The Patlak plot for the lung of the same patient is shown in figure 3. There appears to be no significant accumulation of ^{18}FDG in the lung regions, ki was calculated at 0.49 mL·g^{-1}·h^{-1}. Similar results were found in all CF patients.

Glucose utilisation in the lung is presented in table 2. The mean rate of glucose utilisation was 1.33 μmol·g^{-1}·h^{-1} (95% confidence interval (CI) 0.55–2.10) in CF. By comparison, the mean rate of glucose utilisation in the three sarcoidosis subjects was 2.82 μmol·g^{-1}·h^{-1} (95% CI 2.65–2.99). The median sputum neutrophil count in CF was 13.5×10^6 cells·mL^{-1} sputum (IQR 16.1) or 96% of the total cell count (IQR 3.5). No correlation was found between the rate of glucose utilisation in the lung and sputum-neutrophil levels (r_s=-0.15, p=0.70) and bacterial density (Pearson′s correlation coefficient (r)=0.50, p=0.39) or between glucose utilisation and lung function (r=0.37, p=0.30) in CF patients. However, a negative correlation was found between glucose utilisation and disease severity (r_s=-0.66, p=0.04) suggesting that patients with mild lung disease (forced expiratory volume in one second (FEV1) >60% predicted)

Fig. 2. – a) Representative time-activity curve during the 90-min positron emission tomography scan for a female cystic fibrosis patient aged 26 yrs (patient 8). ●: activity in vein; ○: activity in right lung. b) Quantification of radioactive counts accumulated for 12 5-min frames in the regions of interest drawn over the right lung and vein are shown.

have a higher rate of glucose utilisation than those with moderate/severe disease (FEV1 ⩽60% pred).

There appeared to be no consistent change in ^{18}FDG uptake after antibiotic treatment (fig. 4). No correlation was found between the change in glucose utilisation rates and the change in sputum neutrophil values (r_s=0.29, p=0.53; fig. 5).
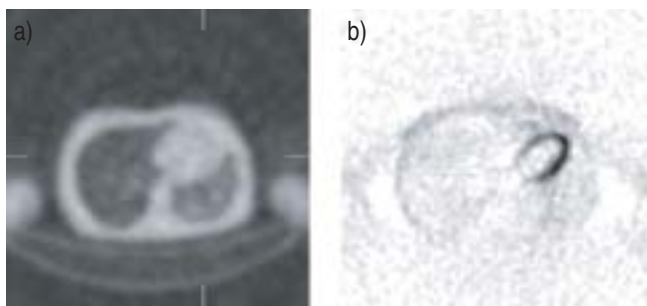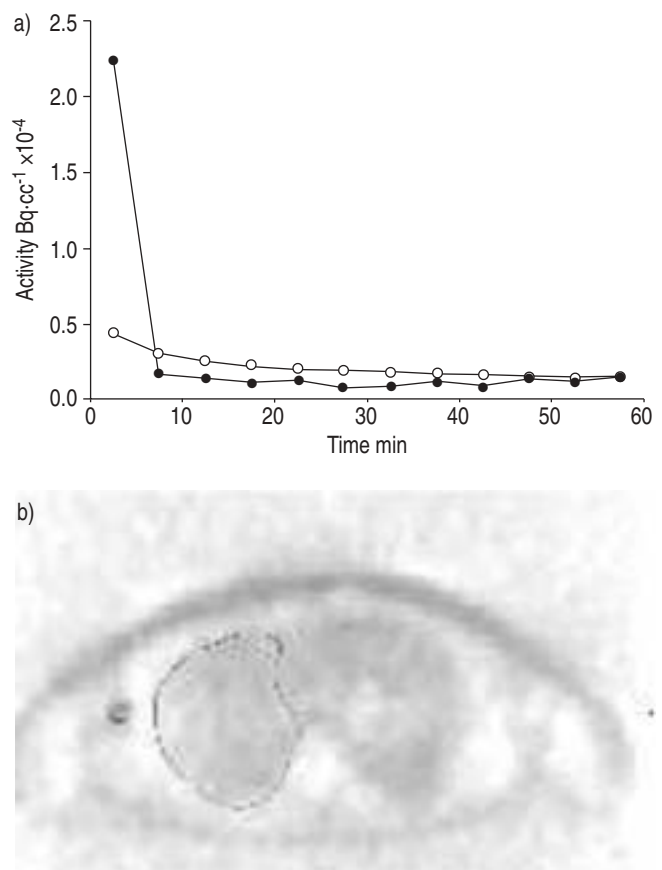
Fig. 1. – Positron emission tomography scan in a female cystic fibrosis patient aged 26 yrs (patient 8). a) The transmission showing the density distribution within the thorax with the lung (low density) in contrast to the heart and chest wall (high density). Patchy areas of increased density are visible throughout the lung. b) The emission scan showing the distribution of radioactivity after intravenous infusion of ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}FDG). Despite the high-sputum neutrophil count (18.0×10^6 cells·mL^{-1} sputum), the image shows no significant accumulation of ^{18}FDG in the lung region. Typical uptake of ^{18}FDG is seen in the heart wall.
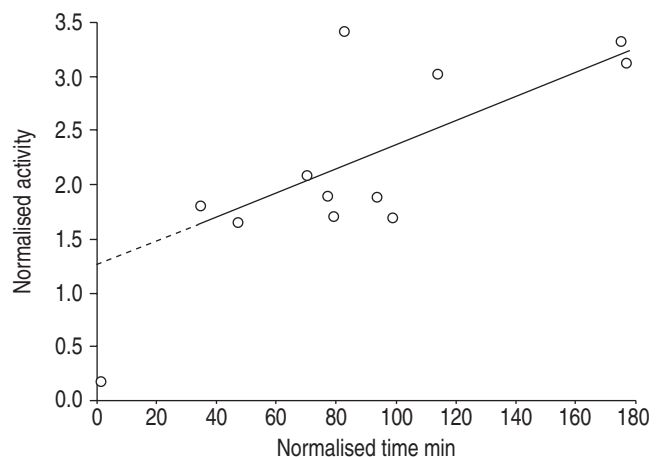
Fig. 3. – Example of the Patlak plots of the right lung reconstructed from the region of interest data for a female cystic fibrosis patient aged 26 yrs (patient 8). The slope of the curve represents a rate of ^{18}F-2-fluoro-2-deoxy-D-glucose uptake (ki) of 0.49 mL·g^{-1}·h^{-1}. The dashed line shows the extrapolation.

Table 2. – ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}FDG) uptake in the lungs of cystic fibrosis (CF) patients and control (sarcoidosis) subjects

Patient	Visit 1				Visit 2			
	FEV1 % pred	ki mL·g^{-1}·h^{-1}	MRglu μmol^{-1}·g^{-1}·h^{-1}	Sputum neutrophil ×10^{6}cells·mL	FEV1 % pred	ki mL·g^{-1} h^{-1}	MRglu μmol^{-1}·g^{-1}·h^{-1}	Sputum-neutrophil ×10^{6}cells·mL$^{-1\#}$
CF								
1	30.0	0.12	0.54	14.0	35.0	0.50	2.28	20.8
2	20.8	0.09	0.39	68.2	20.3	0.098	0.45	62.3
3	53.7	0.03	0.12	12.3	57.6	0.22	1.00	19.0
4	74.0	0.19	0.86	10.0	67.0	0.16	0.74	19.3
5	72.0	0.18	0.85		71.0	0.26	1.18	11.3
6	71.0	0.32	1.46	13.0	81.0	0.16	0.75	6.7
7	68.0	0.68	3.14	14.4	70.0	0.48	2.21	20.4
8	39.2	0.49	2.25	18.0				
9	65.0	0.64	2.94	11.7				
10	41.0	0.16	0.72	48.9	35.0	0.013	0.06	8.1
Sarcoidosis								
1	76	0.62	2.84					
2	86	0.58	2.66					
3	94	0.64	2.96					

% pred: % predicted; ki: rate constant for the metabolic trapping of ^{18}FDG; MRglu: metabolic rate of glucose ultilisation. Patients with sarcoidosis were not given inhaled aminoglycoside therapy and were only scanned once. Two patients (nos 8 and 9) did not complete the study.
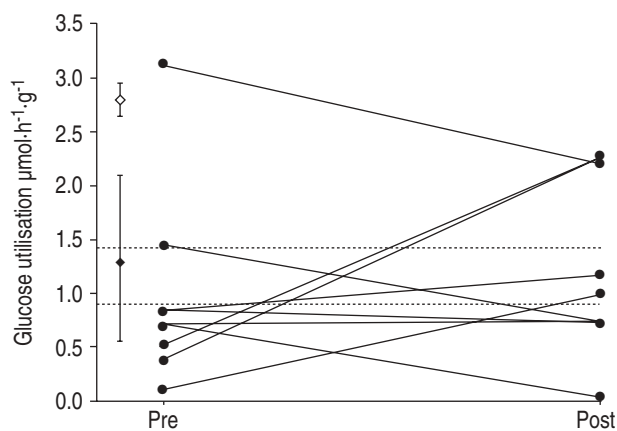

Fig. 4. – Glucose utilisation of the right lung, pre- and post-28 days of inhaled tobramycin therapy 160 mg *b.i.d.* (●). Cystic fibrosis mean glucose utilisation in the lung (◆: 1.3 μmol·g^{-1}·h^{-1}, 95% confidence interval (CI) 0.55–2.10; n=8), Sarcoidosis mean glucose utilisation in the lung (◇: 2.8 μmol·g^{-1}·h^{-1}, 95% CI 2.65–2.99; n=3). The area between the dashed lines represents normal glucose utilisation in the lung of 1.2 μmol·g^{-1}·h^{-1} (95% CI 0.94–1.46).
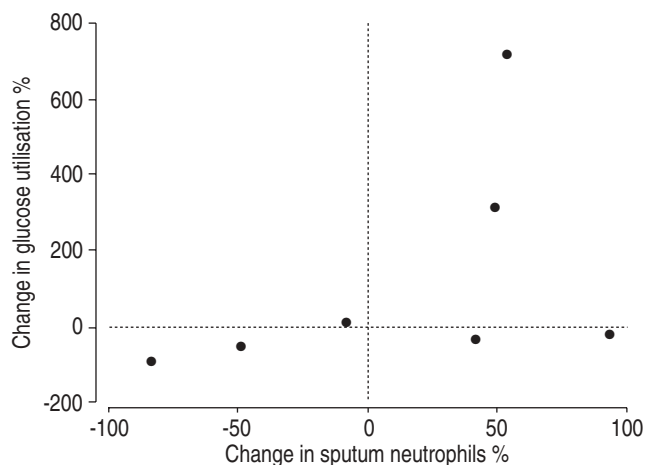

Fig. 5. – Change in glucose utilisation *versus* change in sputum neutrophil counts after 28 days of inhaled tobramycin 160 mg *b.i.d.* therapy. No correlation was found (r_s=0.29, p=0.53).

Discussion

In CF, airway inflammation is characterised by a marked neutrophil influx, high concentrations of pro-inflammatory cytokines for example interleukin (IL)-8 and proteases, such as neutrophil elastase [14]. Neutrophils accounted for 96% of the sputum total cell count (TCC) of 10^6 cells·mL^{-1} sputum. These values are similar to the authors′ previous findings, where the median sputum neutrophil level was 12.9×10^6 cells·mL^{-1} sputum, or 95% of TCC in adult CF patients [31, 32]. Despite the presence of high levels of neutrophils in the airways of CF patients, the authors found that the majority of CF patients had normal or slightly depressed rates of glucose metabolism, with a mean metabolic rate for glucose (MRglu) of 1.33 μmol·g^{-1}·h^{-1} (95% CI 0.55–2.10). In normal lung tissue, glucose utilisation is 1.2 μmol·g^{-1}·h^{-1} (95% CI 0.95–1.46) [33]. The rate of glucose utilisation did not correlate with lung function, lung inflammation or bacterial density.

A similar finding has been reported in patients with bronchiectasis who showed little increase in glucose metabolism. Bronchiectasis is analogous to CF in that patients are chronically infected with *P. aeruginosa*, produce copious amounts of mucopurulent sputum that are difficult to clear and have a persistent airway inflammatory response, which leads to a vicious cycle of inflammation, tissue destruction and respiratory infection [34]. JONES *et al.* [19] examined the relation of metabolic activity to neutrophil emigration in pneumonia and bronchiectasis by measuring ^{111}In-labelled granulocyte emigration into the lungs by γ-scintigraphy. The group also measured neutrophil activity by PET and injected ^{18}FDG. Neutrophil emigration was evident in four of the five bronchiectatic patients they examined, a finding similar to other studies [35, 36]. Despite the ongoing neutrophil migration into the lungs, minimal neutrophil metabolic activity was detected by ^{18}FDG-PET imaging in bronchiectatic patients.

Uptake of ^{18}FDG has been shown to be above normal in sarcoidosis [37], cryptogenic fibrosing alveolitis [33], pneumonia [8, 20, 33], atopic asthma [9] and neonatal acute lung injury [38, 39]. In patients with interstitial lung disease, the mean MRglu was 2.6 μmol·g^{-1}·h^{-1}, reflecting the metabolic activity of the cellular infiltrate associated with the disease [40]. Similar data have been collected from patients with active sarcoidosis (mean MRglu 4.1 μmol·g^{-1}·h^{-1}) [37]. In the present study′s control group, subjects with clinically inactive sarcoidosis had a rate of glucose metabolism above normal (mean MRglu 2.82 μmol·g^{-1}·h^{-1}, 95% CI 2.65–2.99).

The authors′ calculations for glucose utilisation were made on the entire right lung. It is possible, that areas of relatively high ^{18}FDG uptake were present but not in high enough levels to influence the average value for the right lung. In three patients (one with severe lung disease, two with mild disease), small areas of high uptake (twice that of the surrounding lung tissue) were observed that corresponded to a dense area on the transmission scan, thought to be mucus. These localised areas were not present at the second PET scan performed following 28 days of antibiotic therapy, despite an insignificant change in the sputum neutrophil counts. The PET scans from the other CF patients did not exhibit this type of finding, indicating that the Patlak results were representative of the events in the entire lung.

Wide variations in ^{18}FDG uptake were observed among CF patients and within patients that were not attributable to varying degrees of sputum neutrophilia, lung function or changes in inflammation. Although no correlation was found between lung function and glucose utilisation, a significant correlation was found with disease severity, suggesting patients with mild disease have an increased utilisation of glucose compared with those having moderate-to-severe disease. This is in contrast to the authors′ hypothesis that ^{18}FDG uptake is a measure of lung inflammation, specifically neutrophils, and therefore ^{18}FDG uptake would be positively correlated with the degree of sputum neutrophilia. The authors have shown previously that disease severity correlates with the intensity of sputum neutrophilia [32]. Patients with severe lung disease had a significantly higher number of neutrophils residing in their airways than those with mild disease. Several studies have found a similar negative correlation between FEV1 and neutrophil counts [41–43]. Bacterial density did not correlate with ^{18}FDG uptake, which was expected, since the authors′ laboratory has also demonstrated no correlation between sputum neutrophil counts and *P. aeruginosa* density (unpublished data), a finding similar to BAL studies by MEYER *et al.* [42, 44].

There are several possible explanations for this observation in CF. Circulating ^{18}FDG may have been prevented from penetrating into the airway lumen by the presence of increased secretions. The authors did not measure the presence of ^{18}FDG in sputum postimaging. In bronchiectatic patients, JONES *et al.* [19] did find detectable levels of radioactivity in the sputum immediately following the PET scan. Since bronchiectactic patients have similar lung disease features to CF, it is likely that ^{18}FDG also reaches the airway lumen in CF. The negative correlation between glucose utilisation and disease severity suggests that circulating ^{18}FDG may not be able to penetrate into the airways of those patients with moderate-to-severe lung disease. However, FEV1 (% pred), a more objective measure than the categorical grouping of mild (FEV1 >60% of pred) and moderate-to-severe (FEV1 ⩽60% of pred) disease severity did not significantly correlate with glucose utilisation.

Another possible explanation for this observation is that neutrophil activation, or their respiratory burst, is impaired in CF patients. *P. aeruginosa* persists in the lungs despite heavy accumulation of neutrophils in the airway walls and lumen.

This suggests that *P. aeruginosa* may produce substances that suppress neutrophil activity. The bacteria produced two phospholipase-C (PLC) molecules, haemolytic and nonhaemolytic. PLC is induced through phosphate starvation as it functions in phosphate-scavenging pathways. Gram-negative pathogens, for example *P. aeruginosa*, have suboptimal circulating phosphate levels, therefore, PLC is likely to be induced in the CF lung. TERADA *et al.* [45] demonstrated that haemolytic PLC potently suppresses the neutrophil respiratory burst response to bacteria, measured as the rate and amount of oxygen produced. Large quantities of glucose are metabolised during the respiratory burst [46] and when the respiratory burst is inhibited, glucose uptake is also inhibited [47]. Therefore, if the neutrophil respiratory burst is inhibited by haemolytic PLC, ^{18}FDG accumulation in the lung would not occur.

A third hypothesis is that neutrophils are dying upon emigration into the lung. *In vitro* evidence suggests that *P. aeruginosa* induces neutrophil cell death differently from apoptosis. DACHEUX *et al.* [48] showed that coincubation of neutrophils, isolated from human peripheral blood with a CF *P. aeruginosa* isolate, resulted in neutrophil death starting 30 min after infection with 80% of cell lysis occurring within 3 h. Cell death, referred to as oncosis, is characterised by cellular and nuclear swelling, blebbing, vacuolisation and disintegration of the cell membrane. The authors demonstrated that the cytotoxicity of *P. aeruginosa* requires a functional type-III secretion, Exo U-independent system which delivers toxins directly into adjacent host cells. Type-III secretion systems are conserved in many Gram-negative organisms [49]. An isogenic mutant of a CF *P. aeruginosa* isolate, in which the type-III secretion system was nonfunctional, was unable to induce cellular death of neutrophils suggesting oncosis is a type-III secretion-dependent event. If neutrophils are undergoing oncosis, their activation process would not be complete. As a result, glucose metabolism may not be increased. However, their cellular contents, including neutrophil elastase, would be released and available to cause lung damage but phagocytosis of *P. aeruginosa* would not occur, leading to the persistent respiratory infection that is seen in CF and in bronchiectactic patients.

In the eight patients that underwent a PET scan before and after 28 days of inhaled tobramycin, no change in glucose metabolism was observed. In addition no change in sputum inflammatory indices were found, indicating that this antibiotic therapy may not have an anti-inflammatory effect. As a result, the authors could not determine if ^{18}FDG uptake was sensitive to changes in airway inflammation in CF. A previous study of patients with active sarcoidosis found a 69% reduction in MRglu from mean±SD 4.56±1.33 to 1.43±0.11 μmol·g^{-1}·h^{-1}, after treatment with high-dose prednisone [37]. In a longitudinal study of patients with cryptogenic fibrosing alveolitis, MRglu appeared to be predictive of their clinical condition [33]. The authors found that if MRglu remained high over the first year or rose from normal to the high range, the patient′s clinical condition deteriorated. If MRglu remained in the normal range, the patient′s condition remained stable or sometimes improved. These data suggest that ^{18}FDG-PET imaging could be used to monitor disease progression and the efficacy of anti-inflammatory agents in respiratory diseases other than CF and bronchiectasis.

In summary, the results of this study showed that ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography imaging is not useful for the detection and monitoring of lung inflammation in cystic fibrosis. However, the results raise interesting questions with regard to the effectiveness of the host immune system in the lungs of cystic fibrosis patients who are chronically infected with *Pseudomonas aeruginosa*. It is believed that the inflammatory response is defective

and overwhelmed, however, this is the first observation *in situ* that suggests the lung neutrophils may not be functioning normally.

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