Quantifying Pulmonary Inflammation in Cystic Fibrosis with Positron Emission Tomography

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Rationale: Although infection contributes to morbidity in patients with cystic fibrosis (CF), the host inflammatory response is also an important cause of progressive pulmonary function deterioration. Quantifying the inflammatory burden in these patients is challenging and often requires invasive procedures. Positron emission tomographic imaging with [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) could be used as a noninvasive alternative to quantify lung inflammation.

Objective: To determine the relationships among lung [^{18}F]FDG uptake, bronchoalveolar lavage (BAL) neutrophil concentrations, and pulmonary function in patients with CF.

Methods: Twenty patients and seven healthy volunteers were studied. A subset of seven patients also consented to undergo BAL. The uptake of [^{18}F]FDG by the lungs was measured as the net influx rate constant K_i . Patients were stratified by rate of decline in pulmonary function into stable, intermediate, and rapidly declining groups. K_i was compared among groups and was correlated against neutrophil concentrations in BAL fluid.

Results: K_i was significantly elevated ($p < 0.05$) among patients with CF as a whole compared with healthy control subjects (0.0015 ± 0.0009 versus 0.0007 ± 0.0002 ml blood/ml lung/min) but especially in patients with rapidly declining pulmonary function (0.0022 ± 0.0011 ml blood/ml lung/min). K_i correlated positively with the number of neutrophils present in BAL fluid.

Conclusion: Imaging with [^{18}F]fluorodeoxyglucose and positron emission tomography can be used to assess inflammatory burden in patients with CF. Elevations in K_i may be able to identify patients with more aggressive disease and may be useful in monitoring changes in inflammatory burden in response to novel treatments.

Keywords: [^{18}F]fluorodeoxyglucose; neutrophils; pulmonary function

Cystic fibrosis (CF) is a disease characterized by increasing airway obstruction, persistent infection, and neutrophilic inflammation (1). In the majority of patients, respiratory failure develops and is the primary cause of death (2). Neutrophils are the predominant inflammatory cells in the lungs of patients with CF, even in individuals with minimal pulmonary dysfunction, and contribute to the progression of lung disease (2–4). A desirable treatment for CF may be one that tempers the deleterious effects of the neutrophil without impairing host defenses against infection.

As treatments are developed to achieve this goal, efficient outcome measures are needed to evaluate their efficacy. Bronchoalveolar lavage (BAL) is the gold standard for assessing airway inflammation; however, it is invasive, and the lung segments that are sampled may not accurately represent the lung as a whole. Induced sputum and exhaled breath condensates, which are less invasive to obtain, have been difficult to validate as quantitative measures of lung inflammation.

The most common alternative outcome measure that is used in therapeutic tests of antiinflammatory agents in patients with CF is a measure of lung function (usually FEV_1) (5) because FEV_1 has been shown to be a strong predictor of mortality (6). However, changes in inflammatory burden do not always correlate with changes in lung function (7, 8). Even more problematic, given the slow rate of decline in lung function among some patients with CF, is that large numbers of patients must be followed for months to years before differences in treatment groups can be expected, adding to the cost and complexity of designing efficient clinical trials.

Other noninvasive, real-time measures of neutrophilic inflammation in the CF lung are needed. The absence of such measures has been an obstacle to the development and testing of antiinflammatory and antibiotic agents in CF. Because inflammatory processes can be detected by positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose ([^{18}F]FDG), we hypothesized that FDG-PET imaging might be an alternative to BAL or induced sputum for assessing airway inflammation. These measurements are highly quantitative and can be applied to specific lung regions and to the entire lung. The purpose of the current study was to evaluate the ability of FDG-PET imaging to detect and quantify lung inflammation in adult patients with CF and to correlate these measurements to BAL neutrophil concentrations and FEV_1 (9–11).

METHODS

Subject Recruitment

Seven healthy volunteers, ≥ 18 yr old, were recruited to provide a set of normal values for [^{18}F]FDG uptake by the lungs. They had no history of cardiopulmonary disease and had normal chest radiographs, screening bloodwork, pulmonary function tests, and electrocardiograms.

Twenty stable patients with CF, at least 18 yr old, were recruited from the CF clinics at Washington University School of Medicine. Initially, diabetic patients were excluded due to potential competition of high blood glucose levels with [^{18}F]FDG tracer uptake, but these subjects were later included if they met the fasting glucose level criterion (≤ 150 mg/dl). Patients were stratified using criteria reported by Rosenbluth and colleagues (12) (i.e., based on their calculated rate of decline in % predicted FEV_1 into stable [$< 2.3\%$ decline per year], intermediate [2.3 – 4.1% per year], or rapidly [$> 4.1\%$ per year] declining groups) (see the online supplement for other criteria and data collected).

All 20 patients with CF and the seven normal volunteers were imaged using PET and [^{18}F]FDG. A subset of the subjects with CF ($n = 7$) also consented to undergo bronchoscopy with BAL on the day after their PET scan.

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All studies were approved by the Washington University School of Medicine Human Subjects Committee, and all participants gave informed consent.

PET Data Acquisition

All research participants fasted at least 4 h before imaging. After completing a transmission scan, 355 ± 29 MBq (9.6 ± 0.8 mCi) of [^{18}F]FDG were injected intravenously at the start of a 66-min dynamic scan acquisition. Blood samples were collected during this time to determine the "input function" (see online supplement) (13).

PET Data Analysis

Regions of interest were drawn over multiple lung tomographic slices to determine average whole-lung and regional (upper versus lower) lung tissue [^{18}F]FDG uptake. Patlak graphical analysis was used to determine the net rate of [^{18}F]FDG uptake from the blood input function and lung tissue activity curves, measured as the influx constant K_i (slope of the linear regression from the Patlak plot) (14, 15). Corrected K_i (i.e., K_i divided by the initial volume of distribution, the latter represented by the intercept of the Patlak linear regression), glucose metabolic rate ($\text{MRglu} = K_i \times \text{blood glucose level}$), and tissue-to-plasma radioactivity ratio (TPR) (16) were calculated (see online supplement). Lung density was calculated from the attenuation image by standard methods (see online supplement).

BAL and Autoradiography

Standard protocols were used for these procedures (see online supplement).

Statistical Analysis

Group data are expressed as the mean $\pm$ SD. The coefficient of determination (R^2) was calculated for all correlations. The Mann-Whitney rank sum test was used to compare healthy control subjects with all patients with CF and to the subset of patients with CF who underwent bronchoscopy. Standard one-way ANOVA was used to determine differences among stratified groups of subjects with CF and normal control subjects. Repeated measures ANOVA on ranks was used to analyze multiple measurements within the same group. *Post hoc* comparisons were performed using Dunn's method. Statistical significance was set at $p < 0.05$. Sigma-Stat v3.0 (SPSS, Inc, Chicago, IL) was used for statistical testing.

RESULTS

Table 1 lists characteristics of the patients with CF enrolled in the study. They are broadly typical of an adult CF patient

TABLE 1. PATIENT CHARACTERISTICS

	All Patients with CF (n = 20)	Patients with CF Who Underwent PET and BAL (n = 7)
Age, yr	28 $\pm$ 10	37 $\pm$ 10
Sex	9M/11F	4M/3F
FEV ₁ , L	2.3 $\pm$ 0.8	2.3 $\pm$ 0.9
% Predicted FEV ₁	63 $\pm$ 16%	65 $\pm$ 19%
Rate of decline in % predicted FEV ₁	2.7 $\pm$ 2.3	2.2 $\pm$ 2.9
Pancreatic insufficiency	19/20	6/7
Diabetes mellitus	2/20	0/7
Genotype		
Δ F508 (homozygous mutation)	7/20	5/7
Other or unknown	13/20	2/7
Bacterial cultures		
<i>P. aeruginosa</i>	19/20	6/7
<i>S. aureus</i>	13/20	3/7
Medications		
Inhaled tobramycin	13/20	4/7
Azithromycin	7/20	2/7
Other oral antibiotics	4/20	1/7
Steroid therapy	10/20	3/7

Definition of abbreviations: BAL = bronchoalveolar lavage; CF = cystic fibrosis; PET = positron emission tomography.

population, except that only 2 out of 20 patients had diabetes because of the initial restriction on including such patients in the study. Excluding the two diabetic patients did not change the results described here. Characteristics of the group that consented to BAL were not significantly different from those who did not consent.

Examples of the PET images collected are shown in Figure 1. Because the baseline level of [^{18}F]FDG uptake in the lungs is low, especially when compared with uptake in the heart, visual changes in pulmonary uptake are subtle. Figure 2 demonstrates that the quality of the time-activity data collected from lung image regions-of-interest for Patlak graphical analysis is excellent. The Patlak plots (Figure 3), which are based on the time-activity data (such as shown in Figure 2), make it easier to discern differences between the two participants shown in Figure 1 in the rate of lung [^{18}F]FDG uptake (quantified as the slope of each regression plot). Autoradiography of cells harvested from the BAL of one patient (Figure 4) showed that specific uptake of [^3H]deoxyglucose ([^3H]DG) was restricted to neutrophils.

Table 2 shows the various ways of expressing the mean rate of pulmonary [^{18}F]FDG uptake in normal volunteers, in all patients with CF, and in the subset of patients with CF who consented to BAL. The rates of [^{18}F]FDG uptake, as measured by K_i , corrected K_i , and MRglu , were higher in subjects with CF than in healthy volunteers ($p < 0.05$). The TPR was not different between the healthy volunteer group and the group of patients with CF, despite a moderate correlation between K_i and TPR ($R^2 = 0.42$; data not shown). There were no statistically significant differences for any of the methods of expressing K_i between the subset of patients with CF who consented to BAL compared with those who did not consent. No statistical differences in overall lung density (0.34 ± 0.04 g/ml in patients with CF, 0.35 ± 0.03 g/ml in healthy subjects) were present. A moderate correlation between lung density and the Patlak intercept was identified ($R^2 = 0.34$, data not shown).

The mean concentration of total cells collected by BAL was $5.3 \pm 9.5 \times 10^3$ cells/mm³, and the mean concentration of neutrophils was $4.1 \pm 7.2 \times 10^3$ cells/mm³ ($71 \pm 21\%$ neutrophils) (reported normal range in the literature: $0.0\text{--}0.3 \times 10^3$ cells/mm³, $0\text{--}12\%$ neutrophils [17, 18]). The correlation between K_i and numbers of neutrophils recovered by BAL is shown in Figure 5. A similar correlation was found using "corrected K_i " ($R^2 = 0.82$; data not shown). After removing the patient with the highest BAL neutrophil concentration, a strong correlation ($R^2 = 0.95$) was still present between K_i and BAL neutrophil concentrations.

Neutrophil numbers in BAL also correlated strongly ($R^2 = 0.81$) with the rate of decline in pulmonary function (Figure 5). However, in this case, the correlation after removing the patient with the highest BAL neutrophil concentration decreased significantly ($R^2 = 0.44$). In addition, correlations between BAL neutrophil numbers and the individual measurement of FEV₁ or % predicted FEV₁ at the time of PET imaging were even weaker ($R^2 = 0.34$ and 0.37 , respectively; data not shown).

Rates of regional lung [^{18}F]FDG uptake are shown in Figure 6. The rate of uptake in the right upper lung zone in patients with CF was significantly higher than in the right lower lung zone ($p < 0.05$). Given the degree of measured variation, the lower lung zones were not significantly different within or between study groups.

Correlations between K_i from all patients with CF, with or without the intercept correction, and individual measurements of FEV₁ or % predicted FEV₁ were relatively weak ($R^2 = 0.28$, 0.30 , 0.27 , and 0.27 , respectively; data not shown). However, group differences between patients with CF and healthy volunteers were present when the patients with CF were stratified by the rate of decline in pulmonary function (12). The differences

Figure 1. Examples of PET images obtained from a patient with cystic fibrosis (CF) (rapidly declining group, rate of decline = 7.8% decrease in FEV₁/year, $K_i = 32.4 \times 10^{-4}$ ml blood/ml lung/min) and a healthy volunteer. All images are in a transverse orientation at the midventricular level. [¹⁸F]fluorodeoxyglucose uptake by the myocardium (e.g., horseshoe-shaped left ventricle) is seen. Changes in uptake by the lungs over time are more subtle, with increased washout of tracer from the lungs (consistent with less “trapping” of the radiopharmaceutical within lung tissue) in the healthy volunteer when compared with the patient with CF.

between the stable and intermediate groups of patients with CF and the normal subjects were not statistically different, possibly reflecting a lack of power given the size of these subgroups. However, the mean value of the rapidly declining group was significantly higher than that measured among healthy volunteers; of the various means of quantifying the rate of [¹⁸F]FDG uptake in the lungs, these differences were most apparent for K_i and corrected K_i (Figure 7).

DISCUSSION

Although pulmonary infection contributes to the morbidity of patients with CF, it is the intense and persistent host inflammatory response that may account for much of the progressive and virtually inevitable deterioration in lung function (19). Neutrophils are the predominant inflammatory cells in the lungs of patients with CF (20), even in individuals with minimal pulmonary dysfunction. Presumably, these cells play a prominent role in the pathogenesis of pulmonary disease in CF by secreting various proinflammatory mediators, by releasing potent proteases, and by producing reactive oxygen species, all of which contribute to cell injury and lung destruction. BAL fluid samples

obtained from patients with CF have high concentrations of mediators, such as IL-1 β , tumor necrosis factor- α , and IL-8 (21).

Conventional treatment of pulmonary disease in CF is directed at managing infection, using airway clearance techniques and administering systemic and nebulized antibiotics to reduce bacterial stimulation of inflammation in the lungs (22). However, neutrophilic airway inflammation may be an important therapeutic target in CF, and antiinflammatory agents may slow pulmonary deterioration (23, 24), measured as a reduced annual rate of decline in the FEV₁.

Measurement of FEV₁, however, even serially, is a nonspecific measure of airway inflammation at best. Likewise, because pulmonary inflammation in CF is driven primarily by local stimuli, mediators, and chemoattractants and is not a local effect of a systemic inflammatory reaction, systemic markers of lung inflammation are not directly representative of the local inflammatory response. For more direct measures of mediator or cellular function within the airways, an invasive procedure (e.g., BAL) is required.

Induced sputum, another technique for sampling lower airway secretions, is noninvasive but is prone to sampling errors

Figure 2. Time-activity curves obtained from analysis of the images shown in Figure 1 (the analysis shown here includes multiple image time-points not included in Figure 1). Lung tissue radioactivity remains elevated by the end of the imaging session in the patient with cystic fibrosis (CF), whereas activity is declining in the healthy volunteer, consistent with increased trapping (i.e., uptake) of the radiotracer [¹⁸F]fluorodeoxyglucose.

Figure 3. Patlak plots for the same two subjects shown in Figure 1. The slope of the plot for the patient with cystic fibrosis (CF) is noticeably steeper than that of the healthy volunteer, consistent with a greater rate of [^{18}F]fluorodeoxyglucose uptake by the lungs in the patient with CF.

and requires patient cooperation to produce an adequate sample. Noninvasive “anatomic” imaging methods depend on identifying increased densities on routine chest radiographs or computed tomography (CT), but these “infiltrates” are not easily quantified, are nonspecific, and have been difficult to correlate with disease activity.

New tools are needed to measure lung inflammation efficiently, noninvasively, and quantitatively. These new assays would be especially useful as surrogate measures of outcome in clinical trials of novel antiinflammatory therapies for CF. In this regard, PET imaging may be ideal because it is noninvasive and carries with it no additional clinical risk except that due to radiation exposure. The radiation exposure for an FDG-PET study with 370 MBq (10 mCi) of [^{18}F]FDG is 7 mSv (25) for an adult, which is similar to the national average effective dose of 7.8 mSv for chest X-ray CT (26). Indeed, doses from chest CTs can be much higher depending on the technique used (27).

PET imaging with [^{18}F]FDG can detect tissue inflammation in a variety of different clinical settings (28–30), and quantification of inflammation using PET has been applied to the lungs (31, 32). All studies to date suggest that during acute inflammation, increases in lung [^{18}F]FDG uptake are primarily due to the influx of activated neutrophils (33–35). Autoradiography of cells harvested from BAL in the current study is consistent with previous observations in that uptake of [^3H]DG was limited to neutrophils (Figure 3). However, as has been recently shown in mice, lung

Figure 4. Two separate microscopic views (A and B) of autoradiograms of cells harvested from bronchoalveolar lavage fluid from one patient with cystic fibrosis (intermediate group, rate of decline = 1.9% decline in FEV₁/year, $K_1 = 11.4 \times 10^{-4}$ ml blood/ml lung/min) after incubation with [^3H]deoxyglucose and subsequent 8.5 wk-exposure of slides to autoradiographic film. Despite a relatively high background signal, grains are concentrated over neutrophils (enlargements of two example cells, indicated by arrows, shown in insets), indicating specific uptake of the radiotracer by neutrophils.

parenchymal cells likely also contribute significantly to the PET imaging signal (36).

In the current study, the rate of uptake of [^{18}F]FDG by the lungs correlated with the number of neutrophils in the BAL fluid (Figure 5). The rate of uptake among the CF group as a whole was also greater than in normal volunteers and was especially increased in the group of patients with the most accelerated rates of deterioration in pulmonary function (Figure 7).

We also found evidence for regional variation in the lung uptake of [^{18}F]FDG in the patients with CF, with increased uptake in the upper lung zones when compared with the lower lung zones (Figure 6). These results suggest greater inflammation in the more apical portions of the lungs and thus are consistent with studies using chest radiography or high-resolution chest CT showing more lung disease in the upper lung zones of patients with CF (37, 38). The ability to identify and quantify regional pulmonary inflammation is potentially a major advantage of PET imaging techniques over currently available methods of monitoring airway inflammation. It is possible, but remains to be shown, that such regional measurements would also be more sensitive in detecting antiinflammatory effects of novel therapy than global measurements.

The best method for expressing the rate of [^{18}F]FDG uptake by the lungs has not been established. Overall, correlations and group differences were similar in the present study, regardless of whether the rate of [^{18}F]FDG uptake was expressed as K_1 , corrected K_1 , or MRglu. In contrast to recent studies in animals (16), the TPR did not discriminate between healthy volunteers and patients with CF, perhaps because the strength of the correlation between TPR and K_1 in the present study was less strong than in

TABLE 2. PATLAK ANALYSIS OF PET DATA

	K_1 without Correction (ml blood/ml lung/min)	Initial Volume of Distribution of [^{18}F]FDG (Intercept) (ml blood/ml lung)	Corrected K_1 (ml blood/ml lung/min)	Glucose Metabolic Rate (mg glucose/100 ml lung/min)	Tissue-Plasma Radioactivity Ratio (ml blood/ml lung)
Normal subjects (n = 6)	0.0007 ± 0.0002	0.22 ± 0.03	0.0032 ± 0.0008	0.06 ± 0.02	0.29 ± 0.03
All subjects with CF (n = 20)	$0.0015 \pm 0.0009^*$	0.19 ± 0.06	$0.0096 \pm 0.0082^*$	$0.13 \pm 0.08^*$	0.36 ± 0.13
PET and BAL of subjects with CF (n = 7)	0.0015 ± 0.0009	0.19 ± 0.02	0.0079 ± 0.0037	$0.13 \pm 0.06^*$	0.35 ± 0.12

Definition of abbreviations: BAL = bronchoalveolar lavage; CF = cystic fibrosis; [^{18}F]FDG = [^{18}F]fluorodeoxyglucose; PET = positron emission tomography.

*p < 0.05 compared with normal subjects.

Figure 5. (A) Correlation between neutrophil numbers measured in bronchoalveolar lavage (BAL) fluid and K_i as a measure of *in vivo* uptake of [18 F]fluorodeoxyglucose by positron emission tomography. The R^2 value without the “outlier” point representing the highest cell concentration was still high at 0.95. (B) Correlation between neutrophil numbers collected by BAL and lung function, expressed as the rate of decline in % predicted FEV₁. In this case, R^2 decreased to 0.44 if the outlier point is eliminated. PMN = polymorphonuclear leukocytes.

the previously reported animal experiments. The reason for this discrepancy may be related to the range of values (normal versus abnormal) measured in patients versus experimental animals. Regardless, it does not seem that the simpler TPR measurement is a useful method in this clinical setting.

The concept of an intercept correction to K_i was introduced by Jones and colleagues (31) as a correction for differences in the distribution volume of [18 F]FDG among the lungs of patients. Because all PET imaging data are expressed in units of “per ml lung,” differences in the degree of lung inflation, in the absence of any correction, would alter the apparent rate of glucose uptake. In a recent study of acute lung injury in dogs (19), we found that correlations based on corrected K_i were less strong than without the correction. In the current study, neither overall lung density, a surrogate for differences in lung inflation, nor the initial volume of distribution of [18 F]FDG (as measured by the Patlak intercept) was significantly different between the healthy volunteers and patients with CF. Additionally, the correlation between the two was only moderate ($R^2 = 0.34$), suggesting that differences in the [18 F]FDG volume of distribution are not entirely dependent on differences in inflation alone. Finally, consistent with previously reported data (16), the intercept correction did not separate groups more reliably than K_i without the

intercept correction (Figure 7). Because the number of patients studied is still small, however, a final decision about which method for expressing the PET imaging data is optimal in patients with CF should await additional study.

Regardless of which method is used, our data show significant differences between the rate of [18 F]FDG uptake by the lungs of patients with CF versus normal volunteers. This difference was obvious when patients with the most rapid rate of decline in pulmonary function were compared with healthy volunteers (Figure 7). Labiris and colleagues reported that there was no correlation between the uptake of [18 F]FDG and pulmonary function, measured as the FEV₁ (39). However, in a reanalysis of their data, they found that the three patients who had an elevated uptake of [18 F]FDG by PET also had an increased rate of decline in pulmonary function (using the same criteria of Rosenbluth and colleagues [12])—consistent with our “rapidly declining” group—whereas the rate of decline in the seven patients who had no elevation in the uptake of [18 F]FDG was consistent with our “stable” group (Dr. R. Labiris, personal communication). Therefore, our study and the Labiris study suggest that FDG-PET may discriminate between patients with more rapidly declining lung function. Longitudinal studies correlating the PET signal and changes in pulmonary function are required to better evaluate this relationship.

Surprisingly few studies have directly examined the relationship between inflammation in patients with CF and lung function (possibly because of the difficulties in quantifying lung inflammation). Dakin and colleagues studied 22 children less than 4 yr of age with CF and found a weak inverse correlation between numbers of neutrophils in BAL and specific compliance (7). Another study by Nixon and colleagues showed no direct relationship between inflammatory indices by BAL and lung function in 36 children less than 3 yr of age (8). We also found relatively weak correlations with measurements of FEV₁ and % predicted FEV₁ and neutrophil concentrations in BAL. These findings suggest that individual measurements of FEV₁, which may be highly variable depending on acute and chronic factors, may not be useful as a surrogate for testing therapies intended to modify the inflammatory burden in patients with CF. We did find, however, that BAL neutrophil concentrations were significantly correlated with the rate of decline in % predicted FEV₁ (Figure 5), suggesting that the inflammatory burden is higher in patients with higher rates of decline in lung function. These data also lend support to the hypothesis that chronic inflammation leads to the deterioration in lung function in CF.

Figure 6. Means and SDs of regional K_i in right and left upper lung zones (RUZ and LUZ) and right and left lower lung zones (RLZ and LLZ) in patients with cystic fibrosis (CF) and healthy volunteers, using standard ANOVA to compare healthy volunteers and patients with CF and repeated measures ANOVA on ranks to assess differences within groups. * $p < 0.05$ compared with healthy volunteers and compared with the RLZ regions in the patients with CF. + $p < 0.05$ compared with healthy volunteers.

Figure 7. Point plots of K_i (A) and corrected K_i (B), as measures of the rate of [18 F]fluorodeoxyglucose uptake by the lungs, for healthy volunteers (NI) and patients with cystic fibrosis, divided into stable (S), intermediate (I), or rapidly (R) declining groups. Also shown are the mean and SD for each group and the average % predicted FEV₁ in each group (A). The dashed line indicates 2 SD above the mean in the healthy volunteers. In the patients with cystic fibrosis, most values are > 2 SD above the normal mean.

The data in this study suggest that patients with CF with higher rates of decline in pulmonary function have higher numbers of neutrophils in BAL and higher PET-measured rates of [18 F]FDG uptake. Although all three indices of inflammation (BAL neutrophil concentrations, rate of decline in lung function, and the rate of [18 F]FDG uptake) could be used as outcomes measures in clinical trials of antiinflammatory therapy, patient recruitment in trials that require BAL is difficult (only 7/20 patients consented to BAL in this study), and rates of decline in pulmonary function require months to years to determine. An important next step is to demonstrate that the measurements of [18 F]FDG uptake in patients are responsive to antiinflammatory therapy, as was recently demonstrated in mice (40). If this can be accomplished, it would represent a considerable improvement in the efficiency with which such therapies could be evaluated. For instance, based on the data shown in Figure 7, only ~10 patients in the “rapidly declining” group would be required to achieve statistical significance at the $p < 0.05$ level for an antiinflammatory agent that could produce a 50% decrease in the PET imaging signal.

Our data (Figure 7) also suggest that PET could be used to identify patients who may benefit from more aggressive antiinflammatory treatment (i.e., patients with rapidly deteriorating lung function). Whether or not the measure of K_i would be abnormal before or coincident with an accelerated decline in pulmonary function remains to be determined by additional study.

A limitation of this study is that only patients > 18 yr of age were enrolled. This may be significant because pulmonary inflammation and the decline in pulmonary function that is characteristic of CF usually begins in patients younger than 18 yr of age. However, current federal regulations limit the amount of radiation that can be administered to persons under the age of 18 for research purposes (there is no limitation for clinical purposes as long as the benefit of the clinical information obtained outweighs the risks from the radiation exposure). Given the relatively low rate of uptake of [18 F]FDG by the lungs, even in patients with the most rapid rate of decline, it is likely that limiting the amount of radioactivity administered so that persons < 18 yr of age could be studied would result in PET scans of unacceptable image quality.

In conclusion, adult patients with CF have an increased rate of [18 F]FDG uptake in their lungs when compared with uptake in normal volunteers. This difference is especially marked among patients with a rapid decline in lung function during the previous 4 yr. Thus, FDG-PET imaging may be a useful new noninvasive tool to quantify lung inflammation in patients with CF, providing

a means to assess responses to new antiinflammatory treatment strategies.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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