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Analysis of 2-[Fluorine-18]-Fluoro-2-deoxy-D-glucose Uptake Kinetics-in PET Studies of Pulmonary Inflammation

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Abstract

Dynamic positron emission tomography (PET) imaging of the lung using the radiotracer 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (^{18}F -FDG) is an emerging method to assess noninvasively the metabolic activity of pulmonary inflammatory cells. Nevertheless, because of the distinct functional and structural characteristics of inflamed lung tissue standard methods of ^{18}F -FDG analysis can be substantially limited and there is no consensus about the best method for quantification of the ^{18}F -FDG signal for acute or chronic inflammatory lung diseases. This article gives an overview on recent advances in quantitative analysis of ^{18}F -FDG uptake kinetics in non-neoplastic inflamed lung tissue.

Keywords

Radionuclide imaging; positron emission tomography; FDG; lung inflammation; acute respiratory distress syndrome; cystic fibrosis; chronic obstructive pulmonary disease; compartmental modeling

Positron emission tomography imaging (PET) with the radiolabeled glucose analog 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (^{18}F -FDG) has been increasingly used to assess pulmonary inflammation (1–9). Activated inflammatory cells, particularly neutrophils, increase glucose metabolism to much higher levels than non-neoplastic lung tissue (10,11). Therefore, ^{18}F -FDG accumulates in lung regions with neutrophilic inflammation, which can be identified in PET images. ^{18}F -FDG enters inflammatory cells via glucose transporter (GLUT) proteins (12,13), and is phosphorylated by hexokinase to ^{18}F -FDG-6-phosphate, which cannot be further metabolized and remains trapped within the cells.

Measurements of ^{18}F -FDG uptake during acute lung inflammation demonstrated a remarkable specificity for neutrophil activity (14–16), and there is strong evidence that neutrophil priming could be the predominant event responsible for increased ^{18}F -FDG uptake by these cells (10). Recent studies have demonstrated the potential of this new technology in such diverse conditions as pneumonia and bronchiectasis (17), cystic fibrosis (8), endotoxin-induced lung inflammation (4), segmental allergen challenge (18), lung transplantation (2), inflammation in chronic obstructive pulmonary disease and asthma (3,19), as well as in acute lung injury (ALI) induced by oleic acid and endotoxin (16), by mechanical ventilation (20), and by smoke inhalation (6) (Table 1). However, in contrast to the assessment of ^{18}F -FDG uptake by dense tissues such as brain or solid tumors where

quantitative analysis is well defined, assessment of ^{18}F -FDG uptake by the lungs presents a number of challenges, and the best method for quantifying it has yet to be established (8).

One challenge comes from the fact that, in the lungs, the volume fraction occupied by blood may be as much as that occupied by parenchyma. Therefore, blood can be a significant source of ^{18}F -FDG activity unrelated to cellular uptake (Table 1). This is particularly the case during an early phase after intravenous ^{18}F -FDG injection. Moreover, ALI can be associated with dramatically increased permeability or mechanical disruption of the alveolar-capillary membrane, causing alveolar flooding or pulmonary edema (21). In this condition, ^{18}F -FDG could leak into alveolar spaces increasing the apparent rate of ^{18}F -FDG uptake by the lung. Furthermore, because PET data are expressed in units of “per mL lung,” differences in lung inflation affect tissue density and, thus, ^{18}F -FDG distribution volume and apparent rate of glucose uptake (8).

Presently, the methods to quantify ^{18}F -FDG uptake can be grouped in three categories: semiquantitative, graphical analysis, and compartmental modeling. This article gives an overview on recent studies applying these methods in normal and diseased non-neoplastic lungs.

SEMIQUANTITATIVE METHODS

A semiquantitative measure of ^{18}F -FDG uptake is the standardized uptake value (SUV) (27), alternatively called dose uptake ratio (28), calculated as the regional tissue activity concentration, recorded between 45 minutes and 70 minutes after tracer administration, normalized by the injected dose per unit of body weight:

$$\text{SUV} = \frac{\text{tissue activity (mCi/mL tissue)}}{\text{injected dose (mCi)/body weight (kg)}} \quad (1)$$

The SUV is frequently applied in clinical routine for the purpose of tumor characterization, grading, and staging, where it owes its popularity to its computational and experimental simplicity. Some investigators have used SUV to quantify ^{18}F -FDG uptake in non-neoplastic lung tissue (22–24), including settings of pulmonary inflammation (23).

A concern about the SUV method is that it may be a gross oversimplification of a complicated metabolic process (28). Particularly in case of the lungs, where the blood-to-parenchymal tissue ratio is quite high and ^{18}F -FDG in the blood spaces contributes significantly to the activity measured with PET. In fact, SUVs of normal lung in supine patients showed a ventrodorsal and craniocaudal gradient, which was attributed to variations in blood flow and volume, and to increased background activity due to scatter from heart and liver (22). Another confounding factor of SUV is related to the fact that, in the fasting state, ^{18}F -FDG uptake by fat tissue is very low. Because the body weight in equation (1) comprises the weight of all body tissues, SUV can be overestimated in obese persons (24). To account for such variations in a person's fat tissue, a refined method uses lean body weight instead of body weight in the computation of SUV (26). Although acceptable for measurements in liver and spleen, this method has not been found warranted for measurements in the lung (24).

Another simple measure of ^{18}F -FDG uptake is the tissue-to-plasma activity ratio. In animal models of ALI, the tissue-to-plasma activity ratio has shown to correlate with estimates of ^{18}F -FDG net uptake rate determined by graphical analysis (29). However, this result could not be confirmed in cystic fibrosis patients (8).

In conclusion, semiquantitative methods to assess ^{18}F -FDG uptake by the inflamed lung are compelling due to their simplicity, but they lack strong theoretical foundation and further research is required to establish standardized protocols to enhance their accuracy.

GRAPHICAL ANALYSIS

Graphical analysis of ^{18}F -FDG uptake, also referred to as “Patlak analysis” (30), is a computationally effective technique, which has been used in several PET studies of pulmonary inflammation (4,16,17,20,25,26,29). The basic concept is to acquire tissue time-activity data ($C_{\text{PET}}(t)$) by dynamic PET imaging, and to simultaneously measure a time-activity curve of ^{18}F -FDG concentration in blood plasma ($C_p(t)$). Dynamic PET is a series of consecutive images, started simultaneously with a bolus injection of ^{18}F -FDG. Image acquisition times are relatively short at the beginning (<30 seconds) and increase to typically 10 minutes toward the end of a 45- to 75-minute protocol. Coinciding with the images, blood plasma samples are taken from arterial or central venous blood.

A plot of the ratio $C_{\text{PET}}(t)/C_p(t)$ against the ratio of cumulative to instantaneous plasma activity concentration (“normalized time”) becomes linear in the late phase after the tracer injection when the concentration of free (ie, unbound) tracer in blood plasma has equilibrated with that of free tracer in extravascular volumes of distribution (Fig 1). This linear part of the plot is fitted by the equation

$$\frac{C_{\text{PET}}(t)}{C_p(t)} = K_i \frac{\int_{t=0}^t C_p(t) dt}{C_p(t)} + V_{\text{dist}} \quad (2)$$

to identify the ^{18}F -FDG net uptake rate (K_i) and an initial distribution volume (V_{dist}) of the tracer. $C_p(t)$ has been traditionally assessed by sequential manual blood sampling. To circumvent invasiveness, radiation exposure, and costs associated with sequential blood sampling, $C_p(t)$ has also been estimated from a blood pool region defined over the heart chambers or aorta in the dynamic PET images (31–34). However, activity spillover is a concern when $C_p(t)$ is estimated from an image region close to tissue with high ^{18}F -FDG uptake, such as heart muscle or inflamed lung parenchyma. In fact, unless corrected for partial volume effects and activity spillover artifact, the use of a raw image-derived $C_p(t)$ can lead to significant bias in Patlak estimates of lung K_i (31). A $C_p(t)$ correction technique that has been applied for ^{18}F -FDG PET imaging of pulmonary inflammation requires only two central venous blood samples for calibration purposes (31). The authors of that study expect that peripheral rather than central venous calibration blood samples can be used, but refer to further study to validate this assumption.

K_i is a measure of ^{18}F -FDG net uptake per mL lung volume, which includes tissue and air-filled alveolar space. As a result, differences in lung inflation should affect K_i , in addition to the regional metabolic activity. To compensate K_i for differences in pulmonary ^{18}F -FDG distribution volume, Jones et al (3,17) introduced the concept of correcting K_i for the initial volume of distribution, V_{dist} , according to

$$K_{i \text{ corrected}} = K_i \frac{V_{\text{dist normal}}}{V_{\text{dist}}} \quad (3)$$

where $V_{\text{dist, normal}}$ is the V_{dist} found in the lungs of normal subjects (ie, 0.15 mL blood/mL lung). Alternatively, some investigators directly normalized K_i by V_{dist} (2,8,29). However, this normalization was found not to contribute to the interpretation of the ^{18}F -FDG uptake signal during ALI²⁹ nor to the discrimination between normal subjects and patients with cystic fibrosis (8). Moreover, there was only a moderate correlation between overall lung density and V_{dist} , and it was argued that differences in V_{dist} were not just dependent on differences in lung inflation (8). In fact, it is clear that V_{dist} not only reflects extravascular steady-state distribution volume of ^{18}F -FDG, but also includes the blood volume within the tissue (30). As an alternative, K_i has been normalized by the regional tissue fraction (F_{tis}) assessed from a PET-acquired transmission scan (6,20) (ie, by the fraction of the lungs not occupied by air). This approach was found useful to discriminate between normal lungs and those exposed to injurious cyclic hyperinflation (20). Additionally, in an animal model of smoke inhalation exposure, normalization of K_i by F_{tis} did not qualitatively alter the results of increased ^{18}F -FDG uptake, suggesting that regional metabolic activity increase following smoke inhalation was beyond that expected by a mere change in regional inflation (6). Normalization by F_{tis} was found to be more relevant during early changes produced by mild endotoxemia and large tidal volume mechanical ventilation (4).

A yet-unmentioned advantage of the Patlak plot is that it allows for the computation of K_i for small regions of interest, even if these regions are afflicted with high levels of imaging noise. This is because the Patlak plot involves regression over multiple time points of the PET-acquired time-activity curve (Equation 2, Fig 1). Using this property, maps of pulmonary K_i and K_i/F_{tis} were computed in a sheep model of smoke inhalation-induced lung inflammation (9) (Fig 2) to obtain an index of lung K_i heterogeneity. This analysis showed that mere comparison of average lung K_i values could potentially conceal localized increases in ^{18}F -FDG uptake in an inflamed lung. To estimate highest local level of metabolic activity an index ($K_{i \text{ max}}$) was defined as the mean plus standard deviation of the spatial K_i distribution in the lungs. This index had a high correlation with the degree of gas exchange impairment in the inflamed lung (6).

In conclusion, the Patlak plot is a computationally effective technique to assess pulmonary ^{18}F -FDG net uptake rate. This net uptake rate is a combination of blood-to-tissue transport, diffusion from tissue to blood, and phosphorylation by hexokinase. Thus, it provides limited information about individual steps in the ^{18}F -FDG metabolic pathway.

COMPARTMENTAL MODELING

Compartmental modeling of pulmonary ^{18}F -FDG kinetics has been used to estimate rate constants that define the movement of this tracer among the blood and tissue compartments (29,30) (Fig 3). This method is based on original work by Sokoloff and coworkers (35,36) (Fig 3a) and uses the operational equation

$$C_{\text{PET}}(t) = \frac{k_1 k_2}{k_2 + k_3} e^{-(k_2 + k_3)t} \otimes C_p(t) + \frac{k_1 k_3}{k_2 + k_3} \int C_p(t) dt + V_B C_p(t) \quad (4)$$

where $\otimes$ is the convolution operator; V_B is pulmonary blood volume in units of “mL blood/mL lung;” the rate constant k_1 describes blood-to-tissue transfer of ^{18}F -FDG in units of “mL blood/mL lung/minute;” k_2 is the rate of ^{18}F -FDG diffusion back from tissue into the blood in units of “1/minute;” and k_3 describes the rate of ^{18}F -FDG phosphorylation by hexokinase in units of “1/minute.” These parameters are estimated by fitting $C_{\text{PET}}(t)$ and $C_p(t)$ to Equation 4 (eg, with iterative, nonlinear curve fitting algorithms) (37). Basic assumptions of Sokoloff’s model are that 1) the entire unbound tracer is present in a single compartment

acting as precursor pool for the hexokinase reaction, 2) regional glucose metabolism is in a steady state, and that 3) after its phosphorylation the tracer is effectively trapped in the tissue (36).

The advantage of compartmental modeling over graphical analysis is the possibility to assess individual steps in the lung metabolic pathway of ^{18}F -FDG, and to determine the processes that limit ^{18}F -FDG uptake by the tissue (38). Using this approach in an animal model of ALI, Chen et al suggested that pulmonary ^{18}F -FDG net uptake (K_i) may be more a function of transport (k_1) than trapping (k_3) per se (29), and stressed the need for future studies on the contribution of GLUT transporter expression to lung ^{18}F -FDG uptake during neutrophilic inflammation. Note however, because both k_1 and K_i are in units “per mL lung,” it is unclear if correlation of these two parameters solely reflects transport dependency of ^{18}F -FDG uptake, or if this correlation might also be the effect of variations in lung inflation. This concern underlines the need for further studies to elucidate rate-limiting processes for pulmonary ^{18}F -FDG uptake in different settings of ALI.

A concern for applying Sokoloff's model to the lungs is that some of its assumptions might be violated in inflamed, non-neoplastic lung tissue. For instance, high-permeability edema might allow ^{18}F -FDG to leak nonspecifically into spaces functionally far from activated neutrophils (16), which would contradict the assumption that in the tissue, the entire unbound tracer is present in a single compartment acting as precursor pool for the hexokinase reaction. Chen and Schuster concluded that such pulmonary vascular leak, by itself, did not contribute significantly to the ^{18}F -FDG PET imaging signal during their animal model of endotoxin-induced ALI (16). However, in a recent modeling study on ^{18}F -FDG kinetics in the lungs of sheep exposed to ventilator-induced lung injury and smoke inhalation (39), the traditional Sokoloff model failed to fit the dynamic PET data (Fig 4a). In contrast, the PET data could be well described by a novel, lung-specific compartmental model (Fig 4b). In this model (Fig 3b), tracer activity in a lung region of interest (ROI) is considered as the sum of tracer activity in four functional compartments: 1) A blood compartment accounting for the amount of ^{18}F -FDG that is confined to the pulmonary vessels; 2) an extravascular compartment representing the concentration of ^{18}F -FDG in the ROI that constitutes the precursor pool for phosphorylation to ^{18}F -FDG-6-phosphate; 3) an extravascular/noncellular (“edema”) compartment, which accounts for the ROI concentration of ^{18}F -FDG that is not an immediate precursor for phosphorylation; and 4) a metabolite compartment accounting for the ROI concentration of ^{18}F -FDG-6-phosphate. The authors suggested that in their experimental setting a significant component of the lung ^{18}F -FDG PET signal originated from distribution volumes, which were not a direct precursor pool for phosphorylation, and that the new lung-specific model not only predicted ^{18}F -FDG kinetics more accurately than the Sokoloff model, but may also provide new insights in the pathophysiology of lung injury.

CONCLUSIONS

In PET studies of pulmonary inflammation, ^{18}F -FDG net uptake rate K_i is the most frequently used measure to quantify lung metabolic activity, and there are different approaches available to correct K_i for variations in lung inflation. Analysis of ^{18}F -FDG kinetics with a lung-specific compartmental model appears a promising technique to provide new insights in the pathophysiology of lung injury. For both graphical and compartmental modeling techniques, the use of image-derived input function is a prerequisite to make noninvasive analysis of lung ^{18}F -FDG kinetics available in patients with acute and chronic inflammatory lung diseases.

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Figure 1.

Patlak plots generated from dynamic 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (^{18}F -FDG PET) measurements in a control lung (*open symbols*) and a lung with smoke inhalation exposure (closed symbols) in a sheep. Linear regression (*solid lines*) provides lung ^{18}F -FDG net uptake rate (K_i) and initial volume of distribution (V_{dist}). For constant plasma levels of ^{18}F -FDG, the x-axis (normalized time) is identical to true imaging time.

Figure 2.

Maps of 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (^{18}F -FDG) net uptake rate (K_i) and of K_i normalized by regional tissue fraction (K_i/F_{tis}) in a sheep with unilateral exposure to smoke inhalation (9). The smoke exposed left lung appears on the right side of each panel.

Figure 3.

Compartmental models of 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (^{18}F -FDG) tissue kinetics. **(a)** Sokoloff's three-compartment model (34), accounting for ^{18}F -FDG in blood plasma ($C_P(t)$), for the extravascular ^{18}F -FDG precursor pool for phosphorylation ($C_E(t)$), and for concentration of ^{18}F -FDG-6-phosphate ($C_M(t)$), which is irreversibly trapped in the tissue. **(b)** Four-compartment model of pulmonary ^{18}F -FDG kinetics during acute lung injury (36), comprising an extravascular/noncellular ("edema") compartment for ^{18}F -FDG that is not an immediate precursor for hexokinase ($C_{EE}(t)$). k_1 = blood-to-tissue ^{18}F -FDG transfer rate; k_2 = tissue-to-blood transfer rate of ^{18}F -FDG; k_3 = rate of ^{18}F -FDG phosphorylation; k_5 and k_6 = forward and backward transfer rates of ^{18}F -FDG between precursor pool and extravascular/noncellular compartment.

Figure 4.

Compartmental model curve fits of pulmonary 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (^{18}F -FDG) kinetics in the smoke exposed lung depicted in Figure 2. At $t = 0$, a bolus of 10 mCi of ^{18}F -FDG was injected. (a) Curve fit achieved with the traditional Sokoloff model according to Figure 3a, showing a poor model fit during the early phase following tracer bolus injection. (b) Curve fit achieved with the lung-specific model according to Figure 3b. $C_{\text{PET}}(t)$ = positron emission tomography-acquired tissue time-activity curve (heavy line); $C_{\text{model}}(t)$ = model-generated curve fit; V_B = blood volume (mL blood/mL lung).

TABLE 1Reports on ^{18}F -FDG Uptake by Non-neoplastic Lung Tissue

Authors	Experimental Setting	Reference
Miyauchi and Wahl, 1995	Normal lung ($n = 15$)	22
Taylor et al, 1996	Allergen challenge in atopic asthma ($n = 9$)	19
Mamede et al, 2005	Tuberculosis ($n = 10$)	23
Zasadny and Wahl, 1993	Normal lung ($n = 28$)	24
Jones et al, 2003	Normal subjects ($n = 5$)	3
	Chronic obstructive pulmonary disease ($n = 6$)	
	Asthma ($n = 6$)	
Jones et al, 1997	Lobar pneumonia ($n = 5$)	17
	Bronchiectasis ($n = 5$)	
Labiris et al, 2003	Cystic fibrosis ($n = 10$)	25
Brudin et al, 1994	Sarcoidosis ($n = 7$)	26
Chen et al, 2006	Cystic fibrosis ($n = 20$)	8
	Normal subjects ($n = 7$)	
Chen et al, 2006	Endotoxin instillation in normal subjects ($n = 18$)	7
Chen and Schuster, 2004	Acute lung injury in dogs	16
	Normal ($n = 5$)	
	Oleic acid ($n = 7$)	
	Endotoxin ($n = 6$)	
	Endotoxin and oleic acid ($n = 7$)	
Holmes et al, 2005	Segmental allergen challenge in rats ($n = 4$)	18
Schroeder et al, 2007	Smoke inhalation in sheep ($n = 5$)	6
Musch et al, 2007	Ventilator-induced lung injury in sheep	20
	Positive end-expiratory pressure ($n = 6$)	
	Negative end-expiratory pressure ($n = 6$)	
Costa et al, 2010	Mild endotoxemia in mechanically ventilated sheep ($n = 6$)	4