Continuing Education on Imaging Pulmonary Inflammation

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ABSTRACT

Lung inflammatory diseases contribute significantly to the socioeconomic burden of disease. Yet very few new, effective therapies for respiratory disease have been approved for use. A major contributing factor is the lack of biomarkers that can accurately quantify the lung inflammatory burden and that can be used to understand the contribution of lung inflammation to loss in lung function. Molecular imaging approaches can detect and quantify the recruitment and activation of specific immune cells in lung inflammation. We will review the clinical techniques used to image lung inflammation, provide an overview of clinical and emerging positron emission tomography (PET) techniques for quantifying lung inflammation, and discuss potential clinical applications.

Objectives

1. Describe imaging approaches that have been used to measure lung inflammation.
2. Discuss potential applications of $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) PET for quantifying lung inflammation.
3. Gain familiarity with new imaging approaches being used to study lung inflammation.
INTRODUCTION

Inflammatory lung diseases pose a significant socioeconomic burden on society with high morbidity and mortality. Chronic lower respiratory diseases, which include chronic obstructive pulmonary disease (COPD) and asthma, are the third leading cause of mortality in the United States and contribute significantly to societal healthcare costs (1,2). Despite this, the number of new first-in-class drugs being approved for pulmonary indications is disappointingly low, with these drugs incurring the highest research and development costs (3,4). Pulmonary function testing is the mainstay of determining lung disease severity and is the most frequently used primary endpoint for clinical trials in lung disease. However, pulmonary function tests do not directly measure the cause of lung dysfunction and often take at least a year or more to change. Thus, the long periods of observation needed to detect a drug effect increase the costs associated with respiratory drug development.

The lack of quantitative biomarkers that accurately reflect lung disease severity have contributed in part to these higher drug development costs. Extensive efforts have focused on developing blood or lung tissue-based molecularly biomarkers obtained by induced sputum or bronchoscopy (5-7). However, invasive bronchoscopic procedures carry higher complication risks for patients, and peripheral blood samples do not necessarily reflect lung-specific processes. Induced sputum, while noninvasive, samples only the central airways and not the distal alveolar spaces. Therefore, noninvasive, quantitative imaging approaches that can directly measure molecular processes related to lung disease severity could overcome some of these limitations. While all diagnostic imaging modalities can detect the presence of inflammation, these signals are frequently not specific for inflammatory processes. Therefore, molecular imaging techniques that provide inflammation-specific measures could complement the information from existing diagnostic imaging modalities and potentially facilitate basic investigations that can aid in the drug development process.
This review will focus on the molecular and nuclear medicine imaging approaches that have been used to image lung parenchymal inflammation in humans as well as a brief review of the clinical manifestations of lung inflammation on computed tomography (CT), the clinical gold standard method for characterizing lung disease. While many novel, targeted inflammation tracers in preclinical studies have been reported that hold great promise, these will not be reviewed here. Disease-specific data will be presented for COPD, asthma, acute respiratory distress syndrome (ARDS), and interstitial lung diseases (ILDs). Data describing the use of positron emission tomography (PET) with $^{18}$F-fluorodeoxglucose ($^{18}$F-FDG) for measuring lung inflammation in cystic fibrosis have been summarized recently and therefore will not be reviewed here (8).

**Methods for Imaging Lung Inflammation**

**CT Imaging of Lung Inflammation**

Pulmonary inflammation can have varying manifestations depending on the affected compartment, including the airways, vasculature, and/or interstitium. Although the density changes in the lungs themselves are not specific for inflammation, characteristic patterns can be helpful in distinguishing inflammation from other processes. Nemec et al recently described common CT findings and imaging clues for noninfectious inflammatory lung disease, summarized in part below (9).

Airway predominant diseases frequently involve infiltration of the alveoli and alveolar ducts with inflammatory cells, debris, or fluid, as seen in bacterial and organizing pneumonia (representative image in Fig. 1A), as well as aspiration of secretions or food debris. These filled airways cause airspace opacities that can become more confluent and appear as consolidation, with patent airways within these regions appearing as air bronchograms. Characteristic involvement of the small respiratory bronchioles in diseases such as Langerhans cell histiocytosis or smoking-related lung diseases, with pigmented macrophages in respiratory bronchiolitis-associated interstitial lung disease and desquamative interstitial pneumonia, result in centrilobular
and peribronchiolar ground glass opacities and nodules with bronchial wall thickening. The alveolar spaces can also fill with fluid through leaky capillaries such as in ARDS, which is the clinical manifestation of diffuse alveolar damage caused by direct or indirect lung injury. Such leakage can mimic pulmonary edema or pulmonary hemorrhage (Fig. 1B).

ILDs are characterized by inflammation of the interstitial spaces in addition to fibrotic changes with varying degrees of airway involvement. In pulmonary fibrosis, such as usual interstitial pneumonia interstitial inflammation, with or without concomitant fibrosis, results in temporally and spatially heterogeneous reticular subpleural opacities, bronchial wall thickening and dilatation, architectural distortion, and peripheral cystic change or honeycombing, leading to lung volume loss and a restrictive physiology. Nonspecific interstitial pneumonia (Fig. 1C) is characterized more by ground glass opacity related to the symmetrical subpleural interstitial inflammation that is more homogeneous in lung distribution. Interestingly, a fibrotic form of nonspecific interstitial pneumonia can demonstrate several features similar to usual interstitial pneumonia. A recent review of the radiographic manifestations of the spectrum of ILDs is provided for reference (10).

In summary, lung inflammation manifests itself in recognizable and sometimes predictable ways. These methods can be used to differentiate various causes of lung inflammation, but as indicated above, few manifestations are specific for inflammation.

\textbf{18F-Fluorodeoxyglucose (18F-FDG)}

Although \textsuperscript{18}F-FDG uptake itself is not a specific indicator of inflammation, inflammatory processes clearly demonstrate increased \textsuperscript{18}F-FDG uptake, as frequently observed in oncology staging FDG-PET scans. Initial studies using \textsuperscript{18}F-FDG to image lung inflammation focused on measuring neutrophilic recruitment (11,12). However, \textsuperscript{18}F-FDG also accumulates in macrophages (13), lymphocytes (14,15), and eosinophils (16,17). The increased \textsuperscript{18}F-FDG uptake in these activated cell types supports various functions related to their specific immune responses, including cytokine-induced activation of neutrophils and eosinophils (18,19), antigen receptor-
mediated activation of lymphocytes (15,20), and polarization state changes in macrophages (21). Structural cells within the lungs also increase glucose utilization during inflammation (22,23). Therefore, increased lung $^{18}$F-FDG uptake most likely represents a measure of the lungs' integrated inflammatory response in the context of lung inflammatory diseases.

**$^{67}$Ga-Citrate and $^{68}$Ga-Citrate**

Gallium-67 ($^{67}$Ga) is a Group IIIb transition metal similar to ferric ion that binds to multiple iron-binding molecules, including transferrin, lactoferrin, ferritin, and siderophores and has most frequently been used to detect infections. However, $^{67}$Ga localizes in inflammatory processes as well, most likely from binding to lactoferrin within neutrophils (24), though $^{67}$Ga localization to sites of infection and inflammation has been observed in patients with no circulating leukocytes. $^{68}$Ga-citrate, the positron emitting isotope, has similar characteristics to $^{67}$Ga-citrate for imaging infection with the added advantages inherent to PET imaging, including improved spatial resolution and the ability to quantify uptake (25). A number of $^{68}$Ga-labeled peptides are being evaluated for imaging inflammation in preclinical models that have recently been reviewed (26).

**Radiolabeled Leukocytes**

Leukocytes labeled *in vitro* with $^{111}$In-oxine or technetium-99m-exametazime are commonly used in clinical practice to identify infection. $^{18}$F-FDG-labeled leukocytes as well as $^{111}$In-tropolonate in neutrophils and eosinophils have been used for human research investigations (27,28). With all of these approaches, the leukocytes are handled in a manner that avoids activating the leukocytes, thus preserving their ability to response to inflammatory signals in the body for localization. Recently published data with radiolabeled neutrophils have shown that unprimed neutrophils and eosinophils transit quickly through the pulmonary circulation without significant first-pass retention, whereas primed neutrophils are retained significantly in the lungs.
of healthy volunteers (27,29). For radiolabeled eosinophils, the intravascular residence time is 25.2 hours, with margination into the liver, spleen, and bone marrow.

**Somatostatin Receptor Imaging**

Somatostatin receptor (SSTR) imaging, most commonly used for neuroendocrine tumor imaging, is being increasingly used to study inflammatory lung disease. $^{111}$In-pentetreotide, which has been used for decades for imaging SSTRs in neuroendocrine tumors, also images granulomatous inflammatory lesions (30). $^{68}$Ga-DOTANOC, another SSTR imaging agent, has a high affinity for SSTRs 2, 3, and 5, while $^{68}$Ga-DOTATATE has the highest affinity for SSTRs 2, 4, and 5 (31). Variable expression of all five SSTR isoforms have been found on human lymphocytes, monocytes, and macrophages but not on neutrophils (32,33), explaining why inflammatory lesions are frequently seen on somatostatin receptor scintigraphy (32,33). Fibroblasts as well as endothelial cells from tissue samples from IPF patients also express SSTRs, which appear to promote fibroblast activity (34). Thus, SSTR expression in lung disease likely reflects a combination of these processes.

**Translocator Protein Imaging**

The 18 kDa translocator protein (TSPO), previously known as the peripheral benzodiazepine receptor, is upregulated in activated microglia, a macrophage lineage cell in the brain (35). The radiolabeled isoquinolone $^{11}$C-PK11195 binds specifically to TSPO, and its binding correlates with macrophage recruitment in rabbit lungs after silica particle challenge (36). Despite this potential specificity for macrophages, TSPO expression can be found on resting peripheral blood monocytes and neutrophils (37) that increases with endotoxin-induced inflammation, leading to increased $^{11}$C-PK11195 uptake in the lungs (38).
Disease-Specific Investigations

Chronic Obstructive Pulmonary Disease (COPD) and Asthma

COPD is projected to become one of the leading causes of mortality worldwide (3). COPD is a heterogeneous disease that is defined by progressive, irreversible airflow limitation. The lungs’ inflammatory response to the inhalation of particles and gases, particularly from cigarette smoke, is thought to cause lung tissue injury and destruction, thus leading to the development of COPD (39,40). Evidence suggest that macrophages drive the development of COPD, leading to increased neutrophil recruitment in the airways (41,42). Neutrophilia in COPD can persist even after smoking cessation, is associated with areas of greater air trapping and airflow limitation, and correlates with disease severity (43-47). Given the hypothesized link between inflammation and lung tissue destruction, imaging markers that can quantify the lung inflammatory burden in COPD could be more useful in predicting treatment responses to anti-inflammatory interventions than changes in FEV1, which is often the primary endpoint for COPD drug trials.

Asthma affects 300 million people worldwide, causing significant morbidity and leading to high socioeconomic costs (48). Eosinophils are the most common and numerous cell type present in the airways of mild asthma; therefore, asthma has long been regarded an allergic disease caused by T2 lymphocytes. Large cohort analyses, however, have revealed additional clinical and functional phenotypes beyond the classic phenotype of allergic, eosinophilic, steroid-sensitive asthma (49). As many COPD patients also have evidence of asthma, asthma-COPD overlap syndrome is becoming increasing recognized as an independent entity (50). Because the inflammatory phenotype in both COPD and asthma may help guide therapy choices, noninvasive molecular imaging approaches that can differentiate such phenotypes could aid in selecting patients for targeted therapies.

Several small studies have investigated the use of 18F-FDG for monitoring inflammation in both COPD and asthma. COPD studies have focused on quantifying the whole-lung inflammatory
burden in COPD participants and healthy volunteers with $^{18}$F-FDG (51-53). The uptake was quantified using the intercept-normalized Patlak influx constant, $K_i$, to account for differences in lung density as originally described by Jones et al (54). These studies, with a combined 26 COPD participants and 24 age-matched healthy volunteers, demonstrated a similar range of increased intercept-normalized $K_i$ values in the COPD group when compared to healthy volunteers across all studies. Subramanian et al demonstrated in an additional 10 participants with α1-antitrypsin deficiency that the intercept-normalized $K_i$ was unexpectedly not increased in this group relative to healthy volunteers (53). Preliminary results from our own institution, from a protocol approved by our Institutional Review Board and with written consent from participants, further suggest that patients with chronic bronchitis symptomatology have increased $^{18}$F-FDG uptake compared to those without such symptoms (Fig. 2, published in abstract form) (52), in line with the known increased lung inflammation that occurs with chronic bronchitis (55). Together, the available data suggest that $^{18}$F-FDG uptake may be useful in distinguishing inflammatory phenotypes within COPD.

In asthma, $^{18}$F-FDG has been used to image the effects of allergen challenges or exacerbations. Two studies have shown that $^{18}$F-FDG uptake, quantified as the Patlak $K_i$, increased with eosinophilic inflammation induced by segmental allergen challenge in patients with atopic asthma (16,17) but not with nebulized allergen (16). Viral-induced asthma exacerbations also increase pulmonary $^{18}$F-FDG uptake, published in abstract form, though whether this specifically is related to eosinophilic inflammation is unclear (56). Taken together, these data support the potential for using $^{18}$F-FDG to assess for changes in the inflammatory burden in asthma.

The TSPO-targeted tracer $^{11}$C-PK11195 has also been used to image the presence of macrophages in asthma and COPD and compared with $^{18}$F-FDG (51). In this study, $^{11}$C-PK11195 was increased in both patients with COPD and patients with asthma compared to healthy, age-matched controls (51). This was in contrast to the $^{18}$F-FDG signal, which was increased only in
the COPD group. While the presence of increased macrophage numbers has long been known in COPD, emerging evidence points to a larger role for macrophages in asthma than originally appreciated (57). Therefore, the data from this pilot study suggest that $^{11}$C-PK11195 may be useful in imaging the macrophage burden in the lungs.

**Acute Respiratory Distress Syndrome**

ARDS continues to cause significant morbidity and mortality once it develops (58). Although its pathogenesis remains ill-defined, neutrophilic accumulation and activation are prominent and universal features of ARDS and acute lung injury (59). ARDS can be caused by a variety of pathologic conditions, including sepsis, trauma, transfusion of blood products, and ventilator-induced lung injury (60). The common proposed mechanism for ARDS is the persistence of activated neutrophils that release cytokines that destroy lung tissue (61). However, the exact mechanisms by which ARDS develops have yet to be elucidated.

$^{18}$F-FDG has been used extensively to study the kinetics of neutrophil activation and recruitment in ARDS in preclinical models (12,62). Several small studies have further evaluated $^{18}$F-FDG PET in patients with ARDS or at risk of developing ARDS. $^{18}$F-FDG uptake is increased not only in areas of infiltrate or consolidation in patients with ARDS but also in areas of normal-appearing lung (63). This uptake most likely reflects areas at risk of being further injured by ventilation as these more compliant areas are subject to increased stretch, leading to neutrophil recruitment and subsequent lung injury (64). This finding may also explain why low tidal volume ventilation strategies lead to a significant reduction in ARDS mortality as such strategies will reduce the distention of the more normal areas of the lungs (65). Radiolabeled primed and unprimed neutrophils (primed neutrophils being in an enhanced state for responding to inflammatory stimuli) have also been used to demonstrate that normal lungs in healthy volunteers can deprime neutrophils, allowing them to leave the pulmonary circulation (29). In patients with
ARDS, on the other hand, this depriming step fails to occur, leading to increased retention of neutrophils that likely contributes to the development of ARDS. These studies demonstrate the potential for using molecular and targeted cell imaging to better understand the contribution of neutrophilic inflammation to ARDS.

Predicting which ventilated patients will progress to develop ARDS remains challenging. Another small study demonstrated that increased $^{18}$F-FDG uptake precedes the development of clinically defined ARDS and therefore may be a useful method for assessing ARDS risk (66). Our own pilot data corroborated the findings from this pilot study, collected under a protocol approved by our Institutional Review Board and with written consent from legal authorized representatives for the patient. In this study, one patient with a high Lung Injury Predictive Score, a validated measure for predicting acute lung injury risk (67), had increased $^{18}$F-FDG uptake and went on to develop clinical ARDS (Fig. 3). Four others with low Lung Injury Predictive Scores had no increased lung $^{18}$F-FDG and were successfully weaned off of ventilator support without further incident. Newer tracers such as $^{18}$F(+/−)NOS, which targets the inducible nitric oxide synthase and appears specific for iNOS expression in endotoxin-induced lung inflammation in healthy volunteers (68), may also be helpful in identifying early lung inflammation that increases the risk of progression to ARDS. Prospective studies will be needed to validate these initial results and assess the contribution of new, inflammation-targeted tracers for predicting ARDS development.

**Interstitial Lung Diseases**

The ILDs, or idiopathic interstitial pneumonias, comprise a heterogeneous group of diffuse parenchymal diseases characterized by chronic inflammation and fibrosis. Idiopathic pulmonary fibrosis (IPF) is the most common form. ILDs can also develop from multiple other causes, such as connective tissue disorders, sarcoidosis, and certain drug exposures. Chronic inflammation had long been thought to cause the fibrotic changes and structural destruction in ILDs. Therefore, $^{67}$Ga-citrate scintigraphy was used in the past to assess the inflammatory activity in these
diseases and is still used for this purpose in some centers. Increased ⁶⁷Ga-citrate lung uptake is frequently seen in patients with ILDs and has been used to measure the anti-inflammatory effect of steroids. However, reduced ⁶⁷Ga uptake in response to steroid therapy does not correlate with clinical improvement in patients with IPF (69). These results are in line with multiple studies demonstrating the ineffectiveness of steroids and immunosuppression for mitigating ILD progression (70). Therefore, inflammation is less likely to be a causative factor in ILDs.

Growing evidence suggests that the cause of fibrosis is an initial epithelial injury coupled with an inadequate wound-repair response that leads to fibroblast proliferation and parenchymal destruction in ILDs (71). ¹⁸F-FDG uptake is frequently seen in ILDs (Figs. 4 and 5). The more intense ¹⁸F-FDG uptake in areas of honeycombing, in light of data from IPF lung tissue samples showing increased expression of glucose metabolism genes, suggests that increased ¹⁸F-FDG uptake in IPF may reflect an active fibrotic remodeling process (72,73). While the pattern and intensity of ¹⁸F-FDG uptake cannot distinguish between ILD subtypes (74), differences in ¹⁸F-FDG retention using dual time-point imaging predicted poor survival in a small study of 50 IPF patients (75). When accounting for air and blood in regional lung ¹⁸F-FDG uptake, however, fibrotic areas had lower uptake compared to more normal-appearing areas (76). Whether these quantification corrections more accurately represent the underlying biology is unclear in the absence of direct regional validation. Despite this, the data available suggest that ¹⁸F-FDG uptake may reflect fibroblast activity in addition to inflammatory cell activity and thus serve as a marker of treatment response to anti-fibrotic treatments. Further prospective studies will be needed to determine the clinical utility of FDG-PET imaging in ILDs.

Studies with ¹¹¹In-pentetreotide and ⁶⁸Ga-DOTANOC have shown somatostatin receptors (SSTR) expression in IPF (77,78). ¹¹¹In-pentetreotide uptake, expressed as a target-to-background ratio, correlates with altered lung function and the intensity of alveolitis, suggesting a disease-related functional role of SSTRs (78). ⁶⁸Ga-DOTANOC is increased in peripheral and
subpleural HRCT abnormalities in IPF patients, with a strong linear correlation between the SUVmax and disease extent on HRCT (77). Lung $^{18}$F-FDG and $^{68}$Ga-DOTATATE uptake in diffuse parenchymal lung diseases appear to be similar, suggesting that these two tracers image different aspects of the ongoing inflammatory and fibroblastic processes in ILDs (79). Given that a pilot open-label study evaluating long-acting octreotide in patients with IPF showed some improvement in pulmonary function when compared to historical controls (80), SSTR imaging may be a useful method for guiding such treatment decisions.

CONCLUSION

Molecular imaging approaches may serve as useful tools for better understanding the factors that contribute to lung disease progression as well as selecting patients for targeted interventions or therapies. While firm conclusions about the clinical utility of the imaging approaches described above cannot be drawn from the multiple small studies that have been published to date, the data support evaluating these imaging approaches as biomarkers of lung disease activity or severity. As new targeted tracers are developed, molecular imaging will likely advance basic investigations in patients with pulmonary disease that could lead to improved outcomes.

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Figure 1. CT manifestations of inflammatory lung disease. A. Organizing pneumonia is characterized by left lower lobe focal consolidation with peripheral ground glass opacity and air bronchograms. Chronic eosinophilic pneumonia and adenocarcinoma-in-situ can appear similarly. B. Diffuse, confluent ground-glass opacity and interlobular septal thickening with a “crazy paving” pattern in the right lung with lesser involvement of the left lung can reflect multifocal pneumonia, atypical edema pattern, or pulmonary parenchymal hemorrhage. Pleural effusions are also present bilaterally. C. Nonspecific interstitial pneumonia exhibits predominantly peripheral ground glass opacity with fine reticulation and subpleural sparring in the lower lobes, right greater than left. The absence of honeycombing makes usual interstitial pneumonia unlikely.
Figure 2. PET/CT images in COPD and age-matched healthy volunteers in a pilot study assessing reproducibility of $^{18}$F-FDG uptake in COPD lungs. A. Representative positron emission tomography (PET) and computed tomography (CT) images from a healthy volunteer and volunteers with chronic obstructive pulmonary disease (COPD) without or with chronic bronchitis symptoms. The PET images shown are a sum of the last 5 minutes of data from the 60-min dynamic acquisition. The COPD participant without chronic bronchitis had emphysema diffusely throughout both lungs on CT. The COPD participant with chronic bronchitis has more heterogeneously distributed emphysema. Units of intercept-normalized $K_i$ ($K_iN$) = min$^{-1}$. B. All data points in healthy volunteers (N=7), COPD participants without (N=6) and with chronic bronchitis symptoms (N=4). Reported in abstract form in reference 52.
Figure 3. Positron emission tomography and computed tomography images from two patients obtained within 24 hours of being placed on the ventilator. The images on the left demonstrate no $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) uptake within the lungs. The images on the right demonstrate visibly increased $^{18}$F-FDG uptake in both lungs. Standard uptake values (SUV) of the whole lung were not different between the patients, demonstrating the relative insensitivity of SUV for quantifying whole lung inflammation compared to the whole-lung $K_i$, which is higher in the patient on the right. $K_i$ and SUV$_r$ are the $K_i$ and SUV in the 50% of pixels with the highest activity within each region of interest (in white). Images obtained in collaboration with Brian Fuller, MD, Washington University School of Medicine.
Figure 4. High-resolution computed tomography (HRCT) and $^{18}$F-FDG PET-CT in usual interstitial pneumonia. A. Axial high-resolution CT (HRCT) image of the chest demonstrates honeycombing, fibrosis, and traction bronchiectasis, most evident in the lingula. There is also emphysema. B. and C. The axial attenuation-corrected PET and fused PET-CT images demonstrate mild, diffusely increased FDG uptake throughout the lung parenchyma, with more focally increased FDG uptake in the area of honeycombing and fibrosis in the lingula.
**Figure 5.** High-resolution computed tomography (HRCT) and $^{18}$F-FDG PET-CT in interstitial lung disease. A. Coronal maximum-intensity-projection PET image demonstrates diffusely increased FDG uptake in the left lung, with lesser involvement in the right lung. B and C. The axial PET and PET/CT fused images shows heterogeneously increased $^{18}$F-FDG uptake, suggesting active inflammation or possible active fibrosis. D. CT images demonstrate regions of diffuse ground glass opacity with honeycombing, interlobular septal thickening, and bronchiectasis, more pronounced on the right, in the areas of increased $^{18}$F-FDG uptake. While usual interstitial pneumonia was suspected due to the presence of honeycombing, left lung biopsies demonstrated emphysematous changes, subpleural and interstitial fibrosis, and focal organizing pneumonitis, with considerations including hypersensitivity pneumonitis or smoking-related interstitial lung disease.
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