



PET/CT in nononcological lung diseases: current applications and future perspectives

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ABSTRACT Positron emission tomography (PET) combined with computed tomography (CT) is an established diagnostic modality that has become an essential imaging tool in oncological practice. However, thanks to its noninvasive nature and its capability to provide physiological information, the main applications of this technique have significantly expanded.

¹⁸F-labelled fluorodeoxyglucose (FDG) is the most commonly used radiopharmaceutical for PET scanning and demonstrates metabolic activity in various tissues. Since activated inflammatory cells, like malignant cells, predominantly metabolise glucose as a source of energy and increase expression of glucose transporters when activated, FDG-PET/CT can be successfully used to detect and monitor a variety of lung diseases, such as infections and several inflammatory conditions.

The added value of FDG-PET/CT as a molecular imaging technique relies on its capability to identify disease in very early stages, long before the appearance of structural changes detectable by conventional imaging. Furthermore, by detecting the active phase of infectious or inflammatory processes, disease progression and treatment efficacy can be monitored.

This review will focus on the clinical use of FDG-PET/CT in nonmalignant pulmonary diseases.



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PET/CT is an imaging modality that could play a role in evaluation of inflammatory and infectious lung diseases <http://ow.ly/8YGT302aVIS>

Introduction

Positron emission tomography (PET) is a medical imaging modality that enables *in vivo* imaging of the distribution of picomolar concentrations of labelled compounds in the body. The addition of transmission computed tomography (CT) to PET instruments results in images that provide both functional/molecular information and structural details. ¹⁸F-labelled fluorodeoxyglucose (FDG) is a positron emitter with an ~110-min half-life. It permits external imaging using PET and represents the most widely used PET tracer.

FDG-PET was initially introduced to determine the state of physiological and pathological brain functions [1, 2]. Since then, it has become an established imaging modality in the workup for thoracic masses [3, 4], especially primary and secondary lung, pleural and mediastinal tumours. In malignant thoracic conditions, uncontrolled mitotic division of dysplastic tissue is known to be part of its long development process, and

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can be attributed to chronic irritation and inflammation, including that caused by noxious chemicals, parasites or chronic infection.

Following the discovery of FDG as PET tracer, the strength and importance of PET imaging escalated exponentially. Being a glucose analogue, FDG has an affinity towards glucose receptors on cell surface. Overexpression of glucose transporter 1 receptors on cancer tissue surfaces enhances glycolysis and attracts more FDG uptake, where *in vivo* conversion into FDG-6-phosphate by glucose-6-phosphatase takes place. The process essentially reflects the increased metabolic rate of cancer cells [5–9]. This process can be translated using a PET system as an intense uptake of FDG, called metabolic imaging.

In inflammatory and infective conditions, following exposure to aseptic or septic stimulus, a cascade of response will be initiated by the release of local chemokines, interleukins (ILs) and prostaglandins, which are well-known pro-inflammatory mediators. This in turn will regulate the function of “gate keepers” in the venular walls for the migration of neutrophils, monocytes and effector T-cells, facilitated by perivascular macrophages and mast cells. Many authors have elucidated in detail relationship between the inflammatory response, local hyperaemia and hypervascularisation, and uptake of FDG in previous studies [10, 11], supporting the use of FDG-PET/CT in infection and inflammatory conditions [12–15].

In chronic conditions, the polymorphs, granulocytes and macrophages are predominantly involved, and the quantity of energy generated is possibly greater. In these situations, multiple cytokines and growth factors have been shown to facilitate glucose transport without increasing the number of glucose transporters by a mechanism that has not been described in malignant conditions.

KUBOTA *et al.* [11] demonstrated a high accumulation of macrophages and granulation tissues surrounding an abscess in an animal model. Through autoradiography, this group displayed that increased FDG uptake could be found not only in tumour cells but also in the inflammatory cell elements associated with growth or tumour necrosis. Increased capillary permeability at the initial stage of infection could lead to the aggregation of inflammatory cells, like granulocytes, leukocytes and macrophages, at the entry point. This evidence proves that FDG uptake is not specific to malignancy but is also present in infection and inflammation.

In acute inflammation or infection of the chest, FDG uptake occurs primarily by activated neutrophils, whose metabolism (especially during the respiratory burst triggered by the rolling and adhesion phase) is heavily dependent on anaerobic glycolysis, requiring elevated uptake of glucose [16].

PET/CT permits quantification of radioactivity throughout the lungs, and in airspaces and the interstitium, enabling study of the behaviour of inflammatory cells in their native microenvironment. FDG activity has been reported in the course of several experimental and clinical inflammatory or infectious processes in the lungs.

JONES *et al.* [17], for example, used positron emission imaging following injection of FDG to monitor neutrophil metabolic activity *in vivo*, and showed a dissociation between migration and activation of these cells in pneumonia and bronchiectasis. The uptake of deoxyglucose by neutrophils reflected both processes of priming and activation [18]. This supported that neutrophil presence and activation are likely to be orchestrated by pulmonary alveolar and interstitial macrophages.

Thus, it is important for nuclear medicine physicians and radiologists to have a thorough understanding of the cellular mechanisms in relation to the pathophysiology in different clinical settings, including malignancy, infection and inflammatory conditions, to avoid misinterpretation of FDG-PET/CT imaging results that may lead to an inaccurate treatment delivery.

This review article will focus on PET/CT applications in nononcological lung diseases. As the number of clinical applications of FDG-PET/CT grows, it is necessary for nuclear physicians and clinicians to improve their understanding of the difference between inflammatory reaction, infection and malignancy, which is a real challenge.

Acute infectious processes

Tuberculosis and nontuberculous mycobacteria

Assessment of metabolic activity in tuberculosis lesions has been well described with the application of FDG-PET [19–22], although there is still insufficient literature describing evidence-based indications [23].

As a caseating granulomatous disease, tuberculosis can involve any organ by haematogenous spread, lymphatic spread or contiguity. SOUSSAN *et al.* [24] identified two different patterns of tuberculosis on FDG PET scanning: a pulmonary type with a more localised type of infection, and a lymphatic pattern associated with a more intense, systemic infection. However, the most common presentation of active tuberculous lesions involves the lung parenchyma [25, 26].

In particular, tuberculoma typically appears as a fairly discrete nodule or mass with a central caseous necrosis surrounded by a mantle of epithelioid cells and collagen with peripheral inflammatory cell infiltration [27]. There is now growing interest in the potential role of FDG-PET in the functional assessment of inflammatory and infectious pulmonary diseases, including those caused by mycobacteria.

Due to the large number of activated inflammatory cells with high glycolytic rates, active tuberculous lesions usually display an intense FDG uptake, as previously also documented in animals [28].

PET accuracy is very high in identifying active granulomatous foci. In a pilot study, SATHEKGE *et al.* [22] demonstrated that in HIV-negative patients affected by tuberculosis, FDG revealed more extensive involvement when compared with diagnostic contrast-enhanced CT scanning also considering lymphonodal involvement.

However, this infectious process could present different uptake patterns according to the grade of inflammatory activity [20]. YAGO *et al.* [29], for example, reported the case of a “cold” abscess due to *Mycobacterium tuberculosis* with only moderate peripheral and low central FDG activity because it is not accompanied by an inflammatory reaction.

Another important role of this widespread imaging technique is its ability to assess early treatment response. Morphological changes often take significantly longer to be detectable than molecular changes. Thus, the ability to identify active tuberculosis lesions earlier than by conventional radiology has an important impact on patient management. This is particularly relevant in certain clinical settings such as in severely immunosuppressed patients and those co-infected with HIV [30, 31].

FDG-PET allows the rapid assessment of pulmonary and extrapulmonary tuberculosis simultaneously, leading to time saving and cost-effectiveness. However, PET images should be interpreted with caution because of the lack of specificity and inability to clearly distinguish granulomatous disease from malignancy based on standardised uptake values (SUVs). Thus, in view of increasing prevalence, especially in cases of extrathoracic concomitant malignancies, tuberculosis should be considered in the differential diagnosis of FDG-avid thoracic findings, and histopathological confirmation is needed in most cases [32].

Like tuberculosis, recently, an increase in nontuberculous mycobacterial (NTM) infections, especially those by *Mycobacterium avium-intracellulare* complex (MAC), has been recorded. NTM infection is caused by a group of opportunistic bacterial pathogens that are hard to isolate and characterised by nonspecific clinical signs that, thus, could remain underdiagnosed.

Similar to tuberculosis, NTM could have a broad range of radiological patterns including nodular or pseudo-nodular lesions, parenchymal consolidation, cavitary lesions, pleural thickenings, and pleural effusions, or a mixed pattern [33–35].

FDG-PET/CT could reflect the activity and extent of disease by monitoring metabolic activity not only in nodular lesions but also within a broad range of radiologically visible lung lesions in NTM and *M. tuberculosis* infections.

Some authors [36] also propose a greater maximum SUV (SUV_{max}) cut-off of 4.0 to define highly active mycobacterial granuloma lesions and found that average uptake was higher in patients with MAC than those with tuberculosis. Conversely, other authors [37] demonstrated average values of lung lesions were less in NTM than in tuberculosis.

With these findings, it is clear that further investigations are required to identify specific SUV cut-offs, if possible, in order to define potential indications and limitations of PET/CT scanning in both pulmonary NTM and *M. tuberculosis* infections.

Despite these uncertainties, an important aspect of PET/CT imaging is the potential role in assessing not only extent of disease but also evolution and follow-up in both NTM and *M. tuberculosis* patients. Following DAVIS *et al.* [38], who showed the power of this technique to detect and to monitor response to chemotherapy in animals with tuberculous lesions, NAMKOONG *et al.* [39] recently published a case report on the role of FDG-PET/CT in assessing appropriate duration for antimycobacterial therapy in a patient with HIV infection. If confirmed, this application could offer a valuable tool for patient management, especially in complex cases such as AIDS, in which tuberculosis and NTM infections often cause disease dissemination and tend to relapse after treatments.

Other acute lung conditions

Like active granulomatous processes, other infectious diseases (figure 1) and active fibrotic lesions can mimic malignancy, leading to false-positive PET scans; thus, the role of this imaging technique in this setting is limited. However, thanks to its ability to quantitate FDG uptake, FDG-PET could be potentially useful in monitoring the infectious or inflammatory processes, and in determining treatment efficacy [40, 41]. As reported by several authors, FDG-PET imaging has been used to monitor the course of disease after

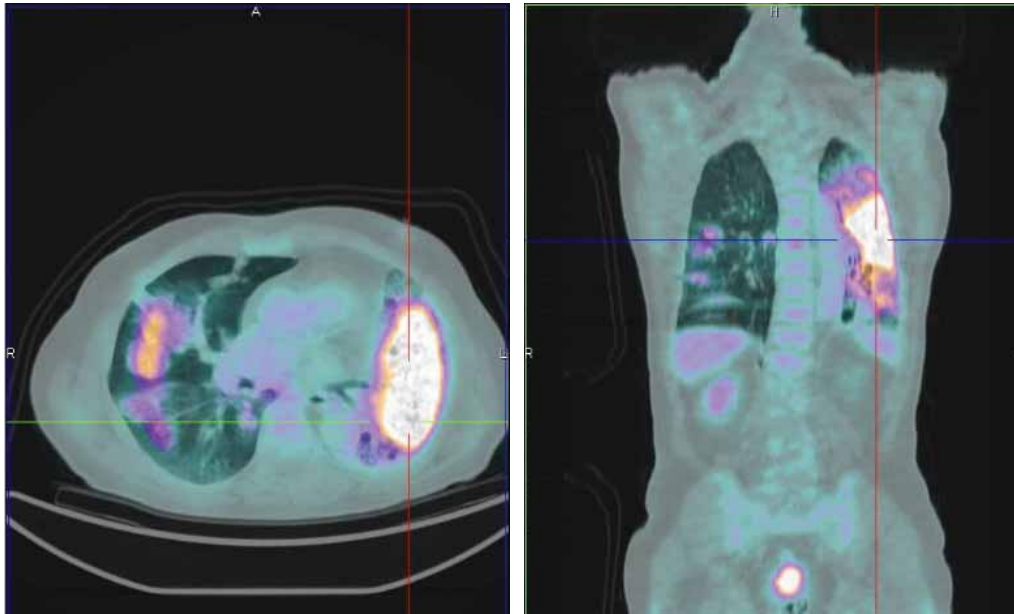


FIGURE 1 Diffuse pulmonary infection in a 71-year-old male before antibiotic therapy. Infectious parenchymal alterations show an intense fluorodeoxyglucose uptake.

treatment in aspergillosis [42, 43] and to evaluate the efficacy of chemotherapy in echinococcosis infection [44]. Conventional imaging techniques are not able to assess parasitic viability in alveolar echinococcosis and the long-term treatment of this pathological condition is very costly. By contrast, FDG-PET could show the disappearance of metabolic activity after treatment and may be useful for timely detection of relapses [45–47].

Similarly, in a clinical study, FDG uptake returned to normal levels after successful antifungal therapy for a lung abscess caused by candidal infection [48] and after therapy for *Pneumocystis jiroveci* pneumonia [49].

Recently, some authors proposed a role of FDG-PET in organising pneumonia (OP), a large group of lung diseases including infectious pneumonia, connective tissue diseases, consequences of solid-organ transplantation, drugs and radiotherapy, or aspiration diseases [50]. OP is an inflammatory disease that can mimic lung cancer by causing a positive FDG-PET. However, this imaging technique may be helpful in predicting prognosis in OP, although histopathological evaluation remains necessary in differential diagnosis [51–53].

Acute or chronic phase of noninfectious inflammatory processes

Besides infectious conditions, PET/CT could also be helpful in the evaluation of noninfectious lung disease. Preliminary studies by JONES *et al.* [16] used FDG-PET to assess neutrophil activity and ^{11}C -PK11195 uptake to assess macrophage accumulation in six patients with COPD, six chronic asthmatics and five age-matched normal control subjects. They found that FDG uptake was greater in COPD than in normal subjects, with no increase in asthmatics.

Thus, they supported PET as a tool to provide an assessment of lung inflammatory cell activity *in vivo*, differentiation of patients with smoking-related COPD from those with asthma, and a potential marker of persistent lung inflammation. This last point is particularly relevant in studies that aim to prevent disease progression in COPD or testing anti-inflammatory treatments.

Pneumoconiosis

Pneumoconiosis is a parenchymal lung reaction to the inhalation and accumulation of noxious dust, such as iron, tin or barium, generally resulting from occupational exposure. Pneumoconioses include coal worker's silicosis, asbestosis and berylliosis. As shown by a number of reports, FDG-PET studies reveal increased uptake in this kind of pneumopathy [54–56]. Inhaled mineral dusts and fibres can cause chronic pulmonary inflammation, often leading to permanent scarring with loss of function by mechanisms not yet fully understood. From a clinicopathological point of view, this reaction could be mainly characterised by fibrosis or by aggregates of particle-laden macrophages with minimal or absent fibrosis, which is typically seen with inert dusts.

PET could represent a valuable tool for monitoring inflammatory processes *in situ*, and quantifying the biochemical and cellular responses involved. This point is particularly relevant in those conditions usually diagnosed in late stages, when therapeutic intervention may not be effective.

As reported in studies performed in animal models of fibrotic and nonfibrotic pulmonary responses to particulate instillation reproducing lung histological alterations typical of pneumoconiosis, PET could investigate different components of the inflammatory response through the use of different tracers.

In particular, FDG could track glucose uptake by neutrophils, which is responsible for an increased signal during pulmonary inflammation associated with lung scarring in cases of persistent high uptake. The radio-ligand ^{11}C -R-PK11195 binds to benzodiazepine-like receptors abundant in macrophages and could point out poor macrophage clearance areas with a higher risk of developing fibrosis [57].

However, for the evaluation of specific kinds of pneumoconiosis, such as silicosis, that are mainly characterised by active fibrosis, a radiotracer that may selectively localise to fibroblasts and not inflammatory cells would be more appropriate. In this setting, as demonstrated by a preliminary study in a rabbit model of induced silicosis [58], PET imaging with labelled fluoroproline could represent the answer to this question, offering the possibility of providing an early and specific diagnosis.

Autoradiographic analysis in animal models showed tritiated or ^{14}C -labelled proline uptake at the alveolar interstitial sites of fibroblast collagen synthesis, suggesting that a major fraction of the proline is taken up as a result of collagen synthesis. Obviously, further analyses are needed to better clarify whether the compound is trapped by the pulmonary interstitial fibroblasts or by the alveolar inflammatory cells as a consequence of inflammatory reaction. A biochemical assay of the fractional amount of fluoroproline sequestered in the lungs as procollagen or an autoradiographic study to evaluate the location of the accumulated fluoroproline at a microanatomic level could be useful to solve this question.

Finally, the increased FDG uptake in nononcological conditions also has to be considered whenever FDG-PET/CT is used in the diagnosis of malignancy in patients with underlying disease such as pneumoconiosis. In this setting, CT imaging probably remains the most appropriate approach.

Sarcoidosis

Sarcoidosis is a multisystem, noncaseating granulomatous disease with unknown aetiology that can affect virtually any organ in the body. It usually starts with mediastinal and hilar lymphadenopathy, followed by lung parenchymal involvement, which is the most frequently affected anatomic site.

Assessment of granulomatous inflammatory activity and extent of chronic sarcoidosis remains a challenge. For this purpose, FDG-PET could contribute significantly.

Due to the presence of activated leukocytes, macrophages and CD4^+ T-lymphocytes together with epithelioid and multinucleated giant cells [59], both pathological lungs and thoracic lymph nodes can show increased FDG uptake (figure 2) [60, 61], and it has been suggested that intensity of FDG uptake may reflect disease activity [62]. In patients with sarcoidosis, FDG-PET has been demonstrated to be superior to conventional nuclear ^{67}Ga -citrate scintigraphy, showing higher sensitivity (90–100%), minimal radiation exposure and shorter acquisition time [62–65]. It was also able to identify occult disease sites that were not detected clinically or by conventional imaging and CT in 15% of patients [59].

Furthermore, in the diagnostic phase, FDG-PET/CT may be a substitute for invasive bronchoalveolar lavage (BAL) [66]. As reported in several studies [61], the extent of metabolic activity in the mediastinum or hila, expressed as SUV_{max} , correlates with the lymphocytosis and $\text{CD4}/\text{CD8}$ ratio, whereas the degree of metabolic activity in the lung parenchyma correlates with the number of neutrophils.

FDG-PET/CT was found to be more sensitive for assessing active sarcoidosis in comparison with serological markers of disease activity (*i.e.* angiotensin-converting enzyme, soluble IL-2 receptor and chitotriosidase), even if the latter correlate well with positive FDG-PET findings [61].

Thus, serological inflammatory markers should be measured first to assess the disease activity in patients with persistent symptoms. However, since negative serological findings do not exclude the presence of inflammatory activity, FDG-PET/CT may be recommended for use as in symptomatic patients [60].

Despite these well described applications (assessment of inflammatory active sarcoidosis in patients with prolonged symptoms, detecting extrathoracic sites of active sarcoidosis, and identifying occult sites and sites suitable for biopsy), FDG-PET/CT could be used for other clinical indications such as planning therapy and monitoring treatment response, and for the follow-up of patients with chronic persistent sarcoidosis.

In fact, the natural course of sarcoidosis in each patient is quite unpredictable and assessment of the degree of inflammatory activity plays a critical role in treatment planning. Identification of patients who need

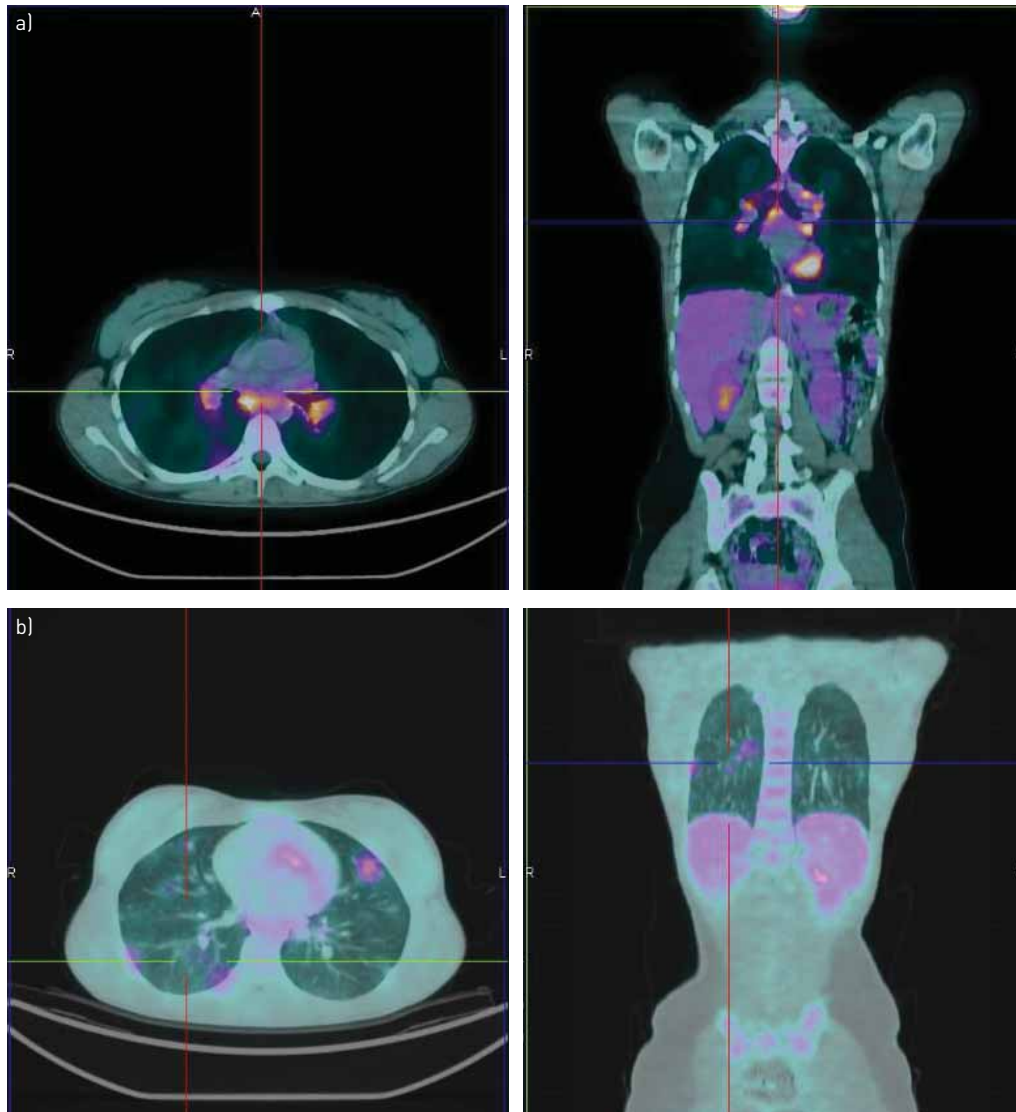


FIGURE 2 Intense fluorodeoxyglucose uptake within a) mediastinal lymph node and b) pulmonary localisations of sarcoidosis in a 45-year-old female.

corticosteroid therapy or in whom the dose of the drug should be modified remains of crucial importance in order to ensure an adequate treatment in those patients in whom progression of the disease may be fatal, but also to reduce significant side-effects related to the inappropriate use of steroids and dosage level.

Furthermore, positive PET findings in patients with thoracic sarcoidosis seem to be associated with impaired lung function [67]: FDG uptake has been shown to correlate significantly with functional markers of disease severity, such as diffusing capacity for carbon monoxide and forced vital capacity [61]. This could give this technique potential prognostic value.

Finally, FDG-PET is also a valuable tool for assessing residual activity in patients with fibrotic pulmonary sarcoidosis [68, 69], contributing to disease monitoring and treatment response evaluation. Interestingly, FDG-PET is also able to detect recurrent sarcoidosis in transplanted lungs [70].

Beyond FDG, other PET tracers could be useful for assessing disease activity in sarcoidosis. YAMADA *et al.* [71] evaluated ^{11}C -methionine (Met) along with FDG in 31 patients with sarcoidosis in a prospective study. These authors noted that the ratio of FDG to Met before therapy could predict the post-treatment course of the disease. In particular, the response rate was higher in the FDG-dominant group (FDG/Met uptake ratio ≥ 2) with respect to the Met-dominant group (FDG/Met uptake ratio < 2) (78% versus 38%, respectively). They concluded that the FDG/Met uptake ratio by PET studies may reflect the differential granulomatous state, suggesting a possible role of this parameter in pre-treatment evaluation of these patients.

In conclusion, FDG-PET/CT imaging allows complete morpho-functional mapping of active inflammatory sites and detection of treatment response in patients with sarcoidosis, especially in certain conditions such as in atypical, complex and multisystem forms of the disease [72].

Obviously, the mandatory prerequisite for all FDG-PET evaluations is an adequate and detailed knowledge about medical history to avoid that sarcoidosis is mistakenly interpreted as malignancy.

Cystic fibrosis

The inappropriate activity of macrophages and neutrophils is known to be involved in some common lung diseases. Cystic fibrosis (CF) represents another example of a pulmonary disease in which neutrophils are the predominant inflammatory cells in the lungs, and contribute to the progression of the illness [73, 74] by secreting various pro-inflammatory mediators, releasing potent proteases and producing reactive oxygen species. Thus, the optimal therapy for CF should be able to counteract the deleterious effects of neutrophil activation without impairing host defences against infection.

CHEN and SCHUSTER[75] showed significant differences between the rate of FDG uptake by the lungs of 20 adult patients with CF *versus* seven adult normal volunteers and, similarly to LABIRIS *et al.* [76], suggested that FDG-PET may discriminate patients with more rapidly declining lung function. In particular, they found that patients with CF and higher rates of decline in pulmonary function have higher numbers of neutrophils in BAL and higher PET-measured rates of FDG uptake.

In patients with CF, they also observed an increased FDG uptake in the upper lung zones compared to the lower lung zones. This regional variation of FDG lung uptake may reflect a greater inflammation in the more apical portions of the lungs, consistent with studies using chest radiography or high-resolution chest CT showing greater involvement in the upper lung zones of patients with CF [77, 78]. Therefore, also in this setting, PET imaging could be used as a noninvasive alternative to identify, quantify and monitor airway inflammation, and thus recognise patients who may benefit from more aggressive anti-inflammatory treatment (*i.e.* patients with rapidly deteriorating lung function).

In fact, the ability to identify and quantify local pulmonary inflammation could be a major advantage of PET imaging techniques over currently available methods of monitoring airway inflammation, potentially detecting anti-inflammatory effects of therapy intervention, as recently demonstrated in mice [79] and in humans [80]. Individual measurements of forced expiratory volume in 1 s, 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. Nevertheless, PET can reveal inflammatory changes in the early phase of the disease preceding structural changes typical of the later stages that are well identifiable on CT scanning.

Acute lung injury and acute respiratory distress syndrome

Acute lung injury (ALI), associated with the acute respiratory distress syndrome (ARDS), is an inflammatory process of the lungs that causes significant morbidity and mortality in critically ill patients [81], with mechanisms that are not fully understood. However, neutrophilic inflammation is a key feature in the majority of cases of ALI. Accordingly, some authors support the hypothesis that tissue injury results from neutrophil activation after an initiating stimulus, and subsequent recruitment of these cells to the lungs, oxidant production and protease release [82]. Differently from nonspecific and sometimes invasive current methods (chest radiography, X-ray CT scans and BAL), FDG-PET imaging could potentially give quantitative information about neutrophil trafficking and kinetics [75], and contribute to our understanding of the pathophysiology of ALI.

SIMON *et al.* [83] first recognised in 1947 that the injured lung is metabolically distinct from the normal lung. Later, FDG-PET was used to evaluate the inflammatory response in some experimental models of lung injury [84–87]. More recently, there has been growing interest in the use of FDG-PET to measure local lung inflammation in ALI with PET [88].

In particular, DE PROST *et al.* [89] tried to determine whether local FDG phosphorylation rate and volume of distribution were sensitive to the initial regional inflammatory response during early ALI. 12 sheep were subjected to homogeneous unilateral surfactant depletion and were mechanically ventilated for 4 h while receiving intravenous endotoxin or not. FDG-PET emission scans were then acquired, and FDG phosphorylation rate and distribution volume were calculated with a four-compartment model. They showed that FDG uptake increased in the endotoxin group and surfactant-depleted sheep, with a topographically heterogeneous distribution. The increase in FDG uptake in the endotoxin group was related both to increases in the FDG phosphorylation rate and to distribution volume. FDG distribution volume increased with infiltrating neutrophils, and phosphorylation rate with the regional expression of inflammatory cytokines such as IL-1 β , IL-8 and IL-10. Thus, they concluded that pulmonary glucidic

metabolism depended on the mechanism of injury, and appeared to be additive to endotoxaemia and surfactant depletion. Analogous studies in patients also confirmed the role of FDG-PET as a valuable imaging biomarker of early lung injury.

The first available case report concerning FDG-PET imaging during ARDS in humans reported an intense metabolic activity in the lungs [90]. FDG uptake rate was increased across the entire lung density spectrum, suggesting that inflammatory cell activation also involves the normally aerated parenchyma [91]. However, the magnitude of FDG uptake and its topographical distribution varied considerably, with some ARDS patients showing activity predominantly in consolidated regions and others in normally aerated regions. RODRIGUES *et al.* [92] studied eight patients with pulmonary contusion. He found a “diffuse” uptake pattern of FDG at 24–72 h after blunt thoracic trauma or pulmonary contusion (*i.e.* involving both nonaerated or poorly aerated, and normally aerated areas on CT) was related to the development of ARDS. However, patients with uptake confined to areas of weak or absent aeration did not subsequently develop ALI. This observation supports once again the predictive value of FDG-PET during the early stages of ALI.

Another radiopharmaceutical that could provide a useful contribution in this setting is represented by ⁶⁸Ga-citrate. In particular, this radiopharmaceutical could explore vascular permeability, which is typically increased in ARDS and not easily detectable by conventional techniques [93, 94].

In conclusion, PET/CT can explore the pathophysiology of ALI/ARDS, allowing noninvasive quantitative assessment of regional pulmonary function and anti-inflammatory therapies effects, and providing a functional evaluation complementary to the morphological changes detectable with conventional radiological imaging techniques. However, whether PET will be used only as a research tool or as part of clinical patient management is still unclear.

Pulmonary Langerhans' cell histiocytosis

Langerhans's cell histiocytosis (LCH) is a rare disease. The aetiology is unknown but LCH is associated with abnormal function of regulatory T-cell, macrophage and/or cytokine-mediated process [95, 96].

Past studies demonstrated the role of immune dysfunction in the pathogenesis of LCH development. Although pro-inflammatory cytokines IL-17A was found in LCH lesions, the association has yet to be validated [97]. Studies suggest the involvement of vascular endothelial growth factor in LCH development while others found evidence of abnormal apoptosis proteins [98–100].

Due to the inflammatory base reactivity involved in LCH development, FDG-PET/CT can be helpful in its clinical assessment, including monitoring response to therapy [101].

Organ transplantation

Clinical evidence on the role of PET/CT in after surgical organ transplantation is lacking, but previous publications have pointed out that FDG-PET/CT could be useful and potentially reduce the number of biopsies required during the follow-up periods of patients after organ transplantation, including transplanted lungs, in distinguishing infection and rejection. In patients with lung transplants, FDG-PET is useful in differentiating pulmonary infection from acute rejection as the latter does not elicit as high a neutrophilic response to infection [102].

Future directions

Differentiating infection from malignancy using FDG-PET/CT could be a hard task. SUV is the most commonly used semiquantitative parameter in routine practice for assessing the degree of FDG accumulation within normal tissues and abnormal lesions. This value represents the radiopharmaceutical activity concentration in a region of interest drawn around a particular structure (in megabecquerels per millilitre) divided by the injected activity (in megabecquerels), in proportion to lean body weight [103]. Due to the numerous factors that can influence SUV (*i.e.* patient size, plasma glucose levels, type of PET camera, duration of uptake time, injected activity and method of image reconstruction), this parameter should be used with caution.

Although SUV measurement is usually used as a semiquantitative method for distinguishing between malignant and benign lesions, it is clear that there is quite often an overlap between SUVs of active inflammatory processes (both of infectious and noninfectious origin) with those of malignant lesions. In the majority of cases, visual assessment of the uptake pattern combined with semiquantitative analysis, clinical presentation and radiological findings allow a more accurate discrimination of benign and malignant findings. Furthermore, in specific clinical settings where there is suspicion of an infectious process, the possibility of supplementing the high sensitivity of FDG-PET with the upper specificity of other nuclear medicine techniques, such as scintigraphy with labelled leukocytes, should be considered.

Dual time-point imaging (DTPI) is recommended as a useful method for distinguishing acute inflammatory reaction from malignancy [104–106]. The rate of dephosphorylation of FDG-6-phosphate is responsible for the different behaviour of FDG uptake between malignant and benign lesions in dual-time FDG-PET imaging [107]: in malignancy, FDG activity will be persistently high after peak uptake in a time activity curve that is unlike that in inflammatory and infective conditions.

However, the real adjunct value of this approach has not been fully clarified yet. Differences in FDG uptake may be related to the type of inflammatory cells within the lesion and DTPI could be less accurate in discriminating chronic granulomatous infection like tuberculosis from cancer. Furthermore, the technique is time-consuming and is not applicable to all patients in the daily routine.

Another important field of investigation is the discovery of new biological radiopharmaceuticals. There are several PET radiopharmaceuticals that have been investigated targeting membrane markers, inflammatory cells, cytokines and vascular reactions in inflammation. Translocator protein, a potential imaging target that is found in macrophages, neutrophils and lymphocytes [108–110], has been used to image inflammatory lung diseases in previous experiments [111].

Besides that, somatostatin receptors (SSTRs) can also be found in abundance in activated lymphocytes and macrophages. Thus, SSTR analogues labelled with ^{68}Ga -citrate, a positron emitter, are ideal candidate radiopharmaceuticals for imaging infectious diseases [112, 113].

Another radiopharmaceutical of interest in this setting is ^{11}C -acetate, which accumulates in tumours but not in inflammatory lesions, thus potentially contributing to differentiating inflammation from neoplasms in patients with tuberculosis. Finally, inflammatory cytokines like cyclo-oxygenase, matrix metalloproteinases, IL-2 and tumour necrosis factor- α are being validated as a potential inflammatory and infective imaging targets in animal models.

In conclusion, PET/CT is a relatively new imaging modality that could play a significant role in the evaluation of inflammatory and infectious lung disease, improving patient management. However, the full potential of this imaging modality remains to be fully exploited and emerging new tracers will be useful for this purpose.

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