Deep-inspiration breath-hold $^{18}$F-FDG-PET/CT is useful for assessment of connective tissue disease associated interstitial pneumonia

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Abstract

Objective: To examine clinical utility of $^{18}$F-flurodeoxyglucose (FDG)-positron emission tomography (PET)/CT for assessment of interstitial lung disease (ILD) in patients with connective tissue diseases (CTDs).

Methods: A total of 69 $^{18}$F-FDG PET/CT scans were conducted under deep inspiratory breath hold (DIBH) conditions in 45 CTD patients with ILD, including 16 dermatomyositis/polymyositis, nine systemic scleroderma and seven rheumatoid arthritis. Intensity and distribution of $^{18}$F-FDG signals in PET/CT were determined by standardized uptake value (SUVmax) and visual score in 18 regions, respectively. ILD was defined as active when immunosuppressive therapy was initiated or intensified.

Results: Both SUVmax and visual score were higher in active phase ($n=32$) than inactive phase ($n=37$) (both $p<0.05$), regardless of the underlying CTD and plain CT findings. The both parameters reduced after initiating or intensifying treatment in the follow-up study of 17 active patients except two died patients who showed increased visual score. Another two died patients showed high visual score (15 and 6/18, respectively). Changing ratio of visual score, but not SUVmax was correlated with KL-6 ($r^2=0.38$, $p<0.05$) and CRP ($r^2=0.52$, $p<0.05$).

Conclusion: The DIBH $^{18}$F-FDG PET/CT procedure sensitively illustrates active ILD lesions in CTD and the extended signal distribution is associated with unfavorable clinical outcome.

Introduction

Interstitial lung disease (ILD) is one of the most common and critical manifestations to determine prognosis in patients with various connective tissue diseases (CTDs) [1,2] The diagnosis of ILD is made concurrently with or after that of the underlying CTD, though ILD can appear as the first symptoms of CTD. Some patients who are diagnosed with idiopathic ILD, especially non-specific interstitial pneumonia (NSIP), are positive for CTD-related autoantibodies despite unsatisfying any sets of criteria for CTD [1–5]. Although the prognosis of CTD-associated ILD (CTD-ILD) is generally more favorable than that of idiopathic ILD [1,2,5,6], the clinical course, severity and therapeutic responses depend on various factors such as the underlying diseases, the radiological and pathological findings. Patients with clinically amyopathic variant of dermatomyositis (DM) have rapidly progressive ILD, which may result in a fatal course despite intensive immunosuppressive therapy [7], whereas ‘‘wait-and-see’’ may be best in some patients having usual interstitial pneumonia (UIP) pattern. Besides heterogeneous features of clinical manifestations, treatment for CTD-ILD is associated with increased risks of drug pneumotoxicity and respiratory infections, which often superimpose additional lesions upon the ILD. Therefore, accurate assessment of lung lesions is critical in management of CTD-ILD.

ILD is categorized according to histopathological findings into UIP, NSIP, organizing pneumonia, diffuse alveolar damage, respiratory bronchiolitis, desquamative interstitial pneumonia and lymphoid interstitial pneumonia. In clinical practice, a multidisciplinary approach based on pathology, clinical symptoms, laboratory tests, imaging examinations, and respiratory function tests, is a gold standard of clinical diagnosis and classification of ILD [3]. High-resolution CT (HRCT) scan, one of the most informative examinations for ILD, illustrates abnormal findings such as ground glass opacity (GGO), reticular opacity (RO), areas of consolidation, honeycombing (HNCB), traction bronchiectasia (TBE), and linear opacity (LO) [8,9]. Accumulating evidence has shown that the findings are closely associated with pathological classifications [3,8–10]. Lung biopsy is useful for differential diagnosis from infection and tumors or assessment of atypical findings of HRCT, though the procedures are often too invasive to conduct in patients with a serious life-threatening condition [10]. Most of the principles for diagnosis and assessment of idiopathic ILD are applicable for those of CTD-ILD [10].

$^{18}$F-flurodeoxyglucose (FDG) positron emission tomography (PET) has developed as an anato-molecular imaging modality for...
the diagnosis and assessment of malignant tumors. Combined PET and CT (PET/CT) systems provide us with both morphological and functional information in a particular lesion. Several reports have shown that 18F-FDG-PET or PET/CT is useful for assessing idiopathic ILD [11–15] and lung lesions in systemic inflammatory disorders [16–22]. However, a standard procedure has not yet been established. Because misalignment between PET and CT images due to respiratory movement causes artifacts under a free breathing (FB) condition, it is often hard to determine signal intensity of tracer uptake in small nodular or diffuse lesions, particularly in the suprarehenic region of lung bases where are most prevalently affected by ILD [23–26].

To minimize respiration related artifacts, deep-inspiratory breath hold (DIBH)-PET/CT technique has been proposed [23]. Comparative analyses have shown the superiority of DIBH-PET/CT over FB-PET/CT in illustrating positive lesions more clearly besides shortening of examination time [25–27]. Multi-bed-position acquisition technique further optimizes the procedure of DIBH-PET/CT [26,28].

This study assessed the CTD-ILD lesions by DIBH-18 F-FDG-PET/CT scan with the multi-bed-position acquisition technique. We found that the procedure was more accurately assess disease activity of ILD than plain CT scan alone and that visual score, which semi-quantitatively evaluated extent and distribution of tracers, reflected disease activity of ILD in CTD patients.

Patients and methods

Patients

We retrospectively collected data of a total of 75 DIBH-18F-FDG-PET/CT scans in 51 patients with rheumatic diseases to assess lung lesions from May, 2008 to August, 2011 in Yokohama City University Hospital. Of them, six patients were excluded because of complications with bacterial pneumonia in five patients and lung cancer in the other one patient. In this study, we analyzed 69 scans in 45 patients (14 men and 31 women; mean age ± SD, 60.6 ± 12.6 y [range, 29–81 y]), who were diagnosed with CTD-ILD.

The underlying rheumatic diseases were diagnosed according to a standard set of criteria for each disease as follows; DM/polymyositis (DM/PM, n = 16) by Bohan and Peter [29], systemic scleroderma (SSc, n = 9) by preliminary criteria for the classification of systemic sclerosis (scleroderma) [30], rheumatoid arthritis (RA, n = 7) by the 1987 American College of Rheumatology (ACR) criteria for RA [31], ant-neutrophil cytoplasmic antibody associated vasculitis (AAV, n = 4) [32], Sjögren syndrome (SS, n = 2) [33], systemic lupus erythematosus (SLE; n = 2) [34], mixed connective tissue disease (MCTD; n = 4) [35], and polymyalgia rheumatica (PMR; n = 1) [36].

The nearest routine laboratory tests and spirometry according to standardization of spirometry proposed by American Thoracic Society/European Respiratory Society within two weeks before the first DIBH PET/CT were analyzed [37]. Based on comprehensive assessments including clinical manifestations, laboratory data and CT findings, ILD was classified as active when new or additional immunosuppressive therapies are required for the ILD, whereas the others were as inactive. The study was approved by the local Institutional Review Board and complied with the Declaration of Helsinki. All patients gave the written, informed consent to DIBH PET/CT scanning.

DIBH18 F-FDG-PET/CT

The procedure of DIBH 18F-FDG-PET/CT was described previously [26]. In brief, patients received an intravenous injection of 340–408 MBq of 18F-FDG after 6 h of fasting followed by an uptake phase of 60 min. The patients were then set up in supine with arm up position just after urination. Helical CT data of the whole-lung area were acquired under a deep inspiratory condition followed by multi-bed PET scanning in 3-dimensional mode with image resolution of 4.0 mm in full width at half maximum. PET data were acquired during eight times of 8 to 15 sec DIBH conditions with 20 s relaxation intervals for approximately 15 min (Supplementary Figure 1). PET images were reconstructed using iterative algorithm (attention-weighted ordered-subsets expectation maximization: 4 iterations, 14 subsets, 7-mm Gaussian filter) with CT-based attenuation correction. All reconstructed images were reviewed and analyzed by voxel-base SP1000 work station (J-MAC systems, Sapporo, Japan) [26].

Imaging analysis

All 18F-FDG PET/CT studies were independently reviewed by one experienced nuclear medicine physician and one internal medicine physician who were unaware of the patient’s status. Disagreements were resolved by consensus. Intensity of 18F-FDG uptake in the region of interest was assessed by the maximum standardized uptake value (SUVmax) according to the following equation: SUVmax = maximal count × calibration factor (kBq/mL)/injected activity (MBq)/body weight (kg). Extent and distribution of positive signals were evaluated by visual score according to CT evaluation in chronic obstructive lung disease shown by Nakano et al. [38]. In brief, each lobe was divided into three regions, internal, intermediate, and external areas in the upper slice 2 cm above the tracheal bifurcation, the middle slice 1 cm below the bifurcation, and the lower slice 2 cm above the right diaphragm (Supplementary Figure 2). The score was determined by numbers of positive signal lesions, where the tracer uptake was more than mediastinum, in total 18 regions.

Statistical analysis

The data were reported as mean ± standard deviation (SD). Paired t-test, Student t-test, and Mann–Whitney’s U test were used to compare two groups, whereas Kruskal–Wallis test was used for three or more groups. Categorical data were analyzed using the Fisher’s exact probability test. Spearman rank correlation coefficient was used to test the association of two parameters. p values less than 0.05 were considered to be statistically significant. All statistical analyses were performed with SPSS software (PASW statistics version 17; IBM Japan, Tokyo, Japan).

Results

Patient characteristics

We analyzed 69 DIBH 18F-FDG-PET/CT scans in 45 patients with CTD-ILD. The underlying diseases were DM/PM in 16 patients, SSc in nine, RA in seven, and others including MCTD in four, AAV four, SS in two, SLE in two, and PMR in one. Clinical characteristics of individual groups were shown in Table 1. Both the underlying rheumatic diseases and ILD were diagnosed concurrently prior to the first PET/CT in 19 patients, while ILD newly developed in four patients with pre-existing CTD. In remaining 22 patients, exacerbation of preexisting CTD-ILD was suspected. Prednisolone (PSL) was given to 21 patients including 12 receiving immunosuppressants such as cyclosporin A and cyclophosphamide, besides three patients receiving monthly intravenous cyclophosphamide without PSL.

Blood sugar levels were less than 150 mg/dl at the PET/CT scan in all patients including users of hypoglycemic agents. There was no significant difference in laboratory data except higher LDH in
PM/DM than in other patient groups \((p = 0.027)\). No significant difference was found in the parameters of the nearest respiratory function test among the disease groups, though not all patients had the test, especially those who were in serious respiratory conditions. Four patients, including three patients with DM and one with PMR, died of ILD-associated respiratory failure within six months after the first examination.

FDG accumulation in the ILD lesions

The highest SUVmax, which represented intensity of FDG uptake in the lesions, was not significantly different among the disease groups \((RA 2.43 \pm 0.68, SSc 2.28 \pm 1.06, PM/DM 2.31 \pm 1.01, others 1.78 \pm 1.03, NS, Supplementary Figure 3A)\), irrespective of treatment. According to the most major finding patterns of the plain CT, the patients were categorized into the three groups; 8 with consolidation, 12 with GGO, and 25 with RO groups including HNCB, TBE, and LO. There was no difference in SUVmax among three groups \((consolidation 2.79 \pm 1.11, GGO 2.70 \pm 1.06, RO 2.54 \pm 1.02, NS)\) \((p = 0.027)\). No significant difference was found in the parameters of the nearest respiratory function test among the disease groups, though not all patients had the test, especially those who were in serious respiratory conditions. Four patients, including three patients with DM and one with PMR, died of ILD-associated respiratory failure within six months after the first examination.

### Therapeutic responses and PET/CT findings

Of 24 patients who had the follow-up PET/CT examination with intervals of 0.5 to 14 months \((2.42 \pm 3.34 months)\), 17 patients including 10 patients with DM were categorized as active and received new or additional immunosuppressive therapy after the first examination. The patients had favorable clinical courses in response to the therapies except two patients who died of progressive respiratory failure caused by ILD with amyopathic variant of DM. The follow-up study revealed that SUVmax was significantly reduced from 2.32 \pm 1.04 to 1.35 \pm 0.80 \((38.31\%)\) after the therapies including two died patients who showed higher SUVmax than the others in both baseline and follow-up examinations \((Figure 3A)\). The post-therapeutic visual score was significantly decreased in 15 survivors \((before 3.67 \pm 2.16, after 1.47 \pm 1.77, p = 0.0003, Figure 3B)\), whereas the score was elevated from 5 to 8, and 4 to 10 in 2 deceased patients, respectively. Another 2 died patients, who did not have the follow-up study, also showed high visual score \((6 and 15)\) and SUVmax \((1.5 and 2.5)\) at the test.

There was a weak correlation between the changing ratio of SUVmax and that of visual score \((R^2 = 0.235)\). In three of five patients having no interval change of visual score, more than 20% of SUVmax reduction was found in response to immunosuppressive therapy. The changing ratio of visual score showed weak to moderate correlation with that of KL-6 \((R^2 = 0.3815, p = 0.015, Figure 3C)\) and CRP \((R^2 = 0.5244, p = 0.001, Figure 3D)\), but not LDH, whereas no correlation was found in the changing ratio of SUVmax and visual score was very weak \((r^2 = 0.22, p = 0.037)\), suggesting that both parameters of PET/CT provided independent information \((Figure 1C)\).

### Extent and distribution of the ILD lesions

Extent and distribution of the ILD lesions were assessed by visual score, which was determined by positive FDG signals in total 18 regions \((Supplementary Figure 2A)\). Representative score 0 to 3 in each lobe are shown in Figure 2. There was no significant difference in visual score among the underlying diseases \((RA 2.43 \pm 0.68, SSc 2.28 \pm 1.06, PM/DM 2.31 \pm 1.01, others 1.78 \pm 1.03, NS, Supplementary Figure 3C)\), and among the plain CT finding patterns \((consolidation 2.38 \pm 1.60, GGO 2.37 \pm 1.60, RO 4.04 \pm 2.85, Supplementary Figure 3D)\). Like SUVmax, visual score was significantly higher in active phase than in inactive phase \((active 4.00 \pm 3.04, inactive 2.70 \pm 2.77, p = 0.035, Figure 1B)\). Scores less than 2 were significantly more common in inactive phase \((20/37)\) than active phase \((9/32, p = 0.026)\). However, correlation between SUVmax and visual score was very weak \((r^2 = 0.22, p = 0.037)\), suggesting that both parameters of PET/CT provided independent information \((Figure 1C)\).

### Table 1. Demographic features and clinical findings of the patients at the first study.

|                  | All    | RA    | SSc   | PM/DM | Others** |
|------------------|--------|-------|-------|-------|----------|
| Number of patients | 45     | 7     | 9     | 16    | 13       |
| Age (years)      | 60.6 ± 12.6 | 65.7 ± 11.4 | 66 ± 9.14 | 56.8 ± 12.2 | 59.4 ± 14.7 |
| Female, n (%)    | 31 (68.9%) | 3 (42.8%) | 7 (87.5%) | 15 (88.2%) | 6 (46.1%) |
| New onset/Recurrence*** | 23/22 | 1/6 | 2/7 | 13/3 | 7/6 |
| Body weight (kg) | 53.4 ± 10.6 | 56.2 ± 7.86 | 51 ± 4.47 | 52.2 ± 12.1 | 54.9 ± 13.1 |
| Blood sugar      | 106.7 ± 21.4 | 100.1 ± 27.3 | 108.6 ± 20.6 | 110 ± 20.6 | 105.2 ± 21.5 |
| WBC (μL)         | 8000 ± 2789 | 6671 ± 1353 | 7175 ± 4135 | 8635 ± 4247 | 8392 ± 3934 |
| CRP (mg/dL)      | 2.9 ± 3.9 | 1.29 ± 0.86 | 2.35 ± 4.22 | 0.76 ± 1.60 | 3.24 ± 6.09* |
| DLH (IU/L)       | 274 ± 122 | 192 ± 45.8 | 230 ± 63.9 | 340 ± 141* | 258 ± 111 |
| SUVmax            | 3.08 ± 1.21 | 2.62 ± 0.97 | 3.38 ± 1.02 | 3.40 ± 1.35 | 2.72 ± 0.89 |
| Visual score     | 0.52 ± 0.27 | 0.32 ± 0.16 | 0.65 ± 0.29 | 0.75 ± 0.27 | 0.65 ± 0.27 |
| SUVmax absolute   | 1.57 ± 0.63 | 1.58 ± 0.97 | 1.57 ± 0.63 | 1.57 ± 0.63 | 1.57 ± 0.63 |
| Visual score absolute | 0.52 ± 0.27 | 0.32 ± 0.16 | 0.65 ± 0.29 | 0.75 ± 0.27 | 0.65 ± 0.27 |
| SUVmax absolute/visual score | 0.52 ± 0.27 | 0.32 ± 0.16 | 0.65 ± 0.29 | 0.75 ± 0.27 | 0.65 ± 0.27 |

Data are shown as mean ± standard deviation (SD) except ratio of female, and new onset/recurrence.

*p < 0.05 in comparison with the other groups.

**Others included ANCA-associated vasculitis and polymyalgia rheumatica.

***Numbers indicate patients who had the examinations at new onset and recurrence of ILD, respectively.
and tacrolimus led to clinical remission, the SUVmax and visual score were reduced from 3.0 to 0.7, and 5 to 0, respectively, with improvement of the plain CT findings. This case was representative as all imaging findings were improved along the clinical course. On the other hand, visual score decreased more than 2 in the follow-up examination of six patients without significant interval changes of the plain CT (Table 2, Case 1 to 6). In a 59-y.o. female with amyopathic variant of DM, abnormal FDG accumulation was reduced (SUVmax 2.7 to 2.0, visual score 5 to 1) after treatment with monthly intravenous cyclophosphamide, oral PSL and tacrolimus, whereas RO and GGO were not remarkably changed in the plain CT scan (Figure 4B, Table 2 Case 2). A 57-y.o female DM patient received two PET/CT examinations with a month interval due to non-productive cough under treatment CsA. Although plain CT findings showed little interval change, visual score and SUVmax in PET/CT were increased 1.8 to 2.5, and 0 to 3, respectively, suggesting progression of ILD (Table 2, Case 7). These findings suggest that PET/CT scan more sensitively detects active ILD lesions than the plain CT in CTD patients.

Figure 1. Association of SUVmax and Visual score with disease activity (A) SUVmax was significantly higher in active phase (2.16 ± 1.04) than inactive phase (1.69 ± 0.84, p = 0.02). (B) Visual score was significantly higher in active phase (4.00 ± 3.04) than inactive phase (2.70 ± 2.77, p = 0.03). Low score (less than 2) was significantly more frequent, inactive phase (20/37) than active phase (9/32, p = 0.026). (C) There was a weak correlation between SUVmax and visual score (R² = 0.22, p = 0.037).

Figure 2. Representative data of visual score. Representative data of visual score in each lobe at a slice are shown. Score 0 and 1 were at the middle slices, whereas Score 2 and 3 were at the lower slice.

Discussion

Disease activity of CTD-ILD is comprehensively determined by a multidisciplinary approach based on clinical symptoms, laboratory data, and imaging modalities including CT scan [3,10]. The present study showed that DIBH 18F-FDG PET/CT visualized active ILD lesions as abnormal FDG accumulation areas. Both intensity and distribution of FDG signals, which were shown by SUVmax and visual score, respectively, were correlated with disease activity of ILD, regardless of the underlying CTD and the plain CT finding patterns. These data suggest that 18F-FDG PET/CT is useful for assessment of ILD activity in patients with CTD as well as those with idiopathic ILD [11–14].

Abnormal findings in the plain CT are not always associated with FDG accumulation. FDG signals reduce along the clinical improvement in response to therapy even when abnormal plain CT findings remain after resolving inflammation. Conversely, FDG signals could be found in normal appearance of pulmonary parenchyma in ILD patients, as shown previously [15], and in a flare-up region of scaring tissues which previously had active inflammation. Especially, FDG signal intensity, expressed by SUVmax in general, is useful for assessment and monitoring of inflammatory activity in a particular region. In addition to signal
intensity, it is important to assess extent and distribution of FDG signals, because ILD lesions spread diffusely and often sporadically in the lung. Indeed, our data revealed that increased visual score was more closely associated with progression of ILD than SUVmax. Visual score, which we first proposed in this study, was very simple and semi-quantitative without special imaging analysis software. Our data suggest that the score is reasonable for assessment of ILD in patients with CTD, though further validation is necessary in other patient groups.

Another technical issue is respiratory movement related artifacts during acquisition of data in PET/CT scan for evaluation of lung diseases. The issue was overcome by applying DIBH with multi-bed-position acquisition technique in this study [26,28]. The procedure contributes to reconstructing clear images in a short-testing time with low-radiation dose of 2 mSv. Most of patients with ILD is tolerable for the DIBH procedure, because acquisition duration in each breath hold and number of breath hold can be adjusted by patient’s respiratory ability. Thus, the procedure of DIBH 18F-FDG PET/CT is very practical as a diagnostic imaging modality for lung diseases including ILD with or without CTD.

There are several limitations in this study, which was designed as a retrospective observational study. First, therapeutic backgrounds were not consistent. More than half of the patients had already received immunosuppressive therapies before the first PET/CT examination. Second, most of the follow-up studies were focused on patients having active ILD at the first examination, because those with inactive ILD were not necessarily monitored as close as those with active ILD. Third, although it is important to compare the PET/CT findings with histopathology, the comparison was not conducted in this study. In addition, positive 18F-FDG
signals are found in other pathological conditions including drug-induced lung injury, infection and cancer, all of which are considered as differential diagnosis from CTD-ILD, particularly during immunosuppressive treatment. Although the signal distribution and coexistence of ILD regions in the other areas were helpful for the differential diagnosis in our representative case, other examinations including bacterial culture, cytology, and laboratory tests under careful monitoring are also necessary to differentiate active ILD from other conditions showing positive FDG signals. Another disadvantage of this procedure is high cost.

In conclusion, the present study demonstrates that DIBH-PET/CT sensitively detects ILD lesions, irrespective of the underlying CTD and plain CT findings. The non-invasive imaging modality is useful for assessment and monitoring of CTD-ILD, especially in patients with serious ILD and unremarkable interval changes in the follow-up CT scans, because it is repeatable.

Conflict of interest
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