Textural analysis demonstrates heterogeneous [^{18}F]-fluorodeoxyglucose uptake in radiologically normal lung in patients with idiopathic pulmonary fibrosis

To the Editor:

Recently, positron emission tomography (PET)–computed tomography (CT) imaging in idiopathic pulmonary fibrosis (IPF) has revealed increased [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) uptake both in fibrotic lung and areas of lung with a normal radiological appearance on high-resolution computed tomography (HRCT) [1, 2]. IPF is characterised by heterogeneous fibrosis at the tissue level, so to gain insight into the early "microscopic" disease process we used established textural features [3, 4] to evaluate heterogeneity of [^{18}F]-FDG uptake in radiologically normal lung in patients with IPF.

Patients with IPF diagnosed according to international guidelines and who had undergone PET-CT imaging for concomitant cancer diagnosis or staging were identified retrospectively in a single interstitial lung disease (ILD) tertiary referral centre. Controls comprised patients without ILD who had undergone PET-CT imaging for lung cancer (control group 1) or extrathoracic malignancy (control group 2).

PET-CT images were analysed by two experienced radiologists. Four 10-mm diameter regions of interest (ROIs) were placed manually in areas of lung with a normal CT appearance, confirmed by measuring lung density. ROIs were placed away from areas of high FDG uptake (concomitant tumour, mediastinum and diaphragm) to avoid spill-over. [^{18}F]-FDG uptake (standardised uptake value (SUV)) and textural features were extracted within each ROI using XD (Mirada Medical Ltd, Oxford, UK) and proprietary software [5]. Mean and maximum SUV were normalised using body weight. 20 textural features were extracted from each ROI, including first order statistics (FOSs) derived from the grey-level intensity distribution, a measure of grey-level uniformity derived from the Laplacian of Gaussian (LoG) technique for a range of filter sizes (in millimetres), and Laws texture features using two-dimensional convolution masks [3–5]. Paired t-tests were used to compare fibrotic and normal lung in IPF patients. Unpaired t-tests were used to compare normal lung in IPF and controls, using a Bonferroni-corrected α of 0.0025 (0.05/20). Data are presented as mean±SD.

49 PET-CT scans were identified from 16 patients with IPF (13 men and three women; mean±SD age 74.1±10.2 years, forced vital capacity 87±12% predicted and transfer factor of the lung for carbon monoxide 46±14% predicted), 17 lung cancer controls (10 men and seven women; age 61.3±16.4 years) and 16 extrathoracic malignancy controls (nine men and seven women; age 64.5±12.4 years). Lung cancer was the most common reason for PET-CT imaging in IPF patients (11 out of 16). Most extrathoracic malignancy controls had lymphoma or melanoma (11 out of 16).

Areas of radiologically established fibrosis in IPF patients exhibited higher SUV compared to radiologically normal lung in the same patient (maximum SUV 2.1±0.5 *versus* 1.0±0.3, p<0.001; mean SUV 1.3±0.4 *versus* 0.8±0.3, p<0.001).

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Textural analysis demonstrates increased heterogeneity of [^{18}F]-FDG uptake in normal lung (on CT) in patients with IPF. Molecular imaging of the lungs using PET can be used to study early disease in IPF before CT abnormalities are apparent. http://ow.ly/T82W30lGU0X

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Radiologically normal lung on CT was confirmed by measuring lung density, showing identical Hounsfield units in IPF and controls (data not shown). There were no differences between the two control groups in maximum or minimum SUV in radiologically normal lung. On PET imaging, the SUV in radiologically normal lung in IPF patients was significantly higher than normal lung in pooled controls (maximum SUV 1.0±0.3 *versus* 0.7±0.2 respectively, p=0.002; mean SUV 0.8±0.3 *versus* 0.6±0.2, p=0.001).

We found significant differences in heterogeneity of the PET [^{18}F]-FDG signal in normal lung between IPF patients and controls in six textural features (figure 1): LoG uniformity with a 3.84-mm filter (0.77±0.12 *versus* 0.92±0.10 respectively, p<0.0001); LoG uniformity with a 6.19-mm filter (0.87±0.12 *versus* 0.98±0.05, p<0.0001); Laws texture L5E5 mean ($5.9\pm2.8\times10^4$ *versus* $2.8\pm1.4\times10^4$, p<0.0001); Laws texture L5L5 standard deviation ($2.3\pm1.5\times10^6$ *versus* $1.1\pm0.6\times10^6$, p<0.001); Laws texture L5E5 standard deviation ($2.1\pm1.2\times10^4$ *versus* $1.0\pm0.52\times10^4$, p<0.0001); and FOS standard deviation (310±199 *versus* 139±77, p<0.0001). These textural features indicate higher variability in signal intensities within the ROIs in radiologically normal lung in IPF.

IPF is a patchy disease at the tissue level, with areas of new and established fibrosis interspersed with histologically normal lung. As IPF progresses over time, fibrosis spreads to involve previously unaffected lung. Increased [^{18}F]-FDG uptake in radiologically normal lung in patients with IPF [2] has been proposed to reflect increased metabolism in inflammatory cells, erythrocytes or fibroblasts in early injury or fibrosis before structural lung changes become apparent on HRCT [6–8]. Our finding of heterogeneous [^{18}F]-FDG uptake demonstrated by textural analysis in radiologically normal lung in IPF patients supports use of PET imaging to noninvasively identify early "microscopic" disease. We cannot say whether the heterogeneous [^{18}F]-FDG signal represents early injury, inflammation, fibrosis or other processes that would require histological correlation. Redistribution of pulmonary blood flow to normal lung is an unlikely explanation for our findings because there was no increase in CT density, the IPF patients did not have severe disease and we would not expect blood flow to generate a heterogeneous PET signal. A limitation of the present study was the relatively small (10 mm) ROIs which were necessary to avoid spill-over effect and to target only lung that was normal on CT. Our results require confirmation in other populations with early pulmonary fibrosis, including patients with rheumatological disease or subjects in

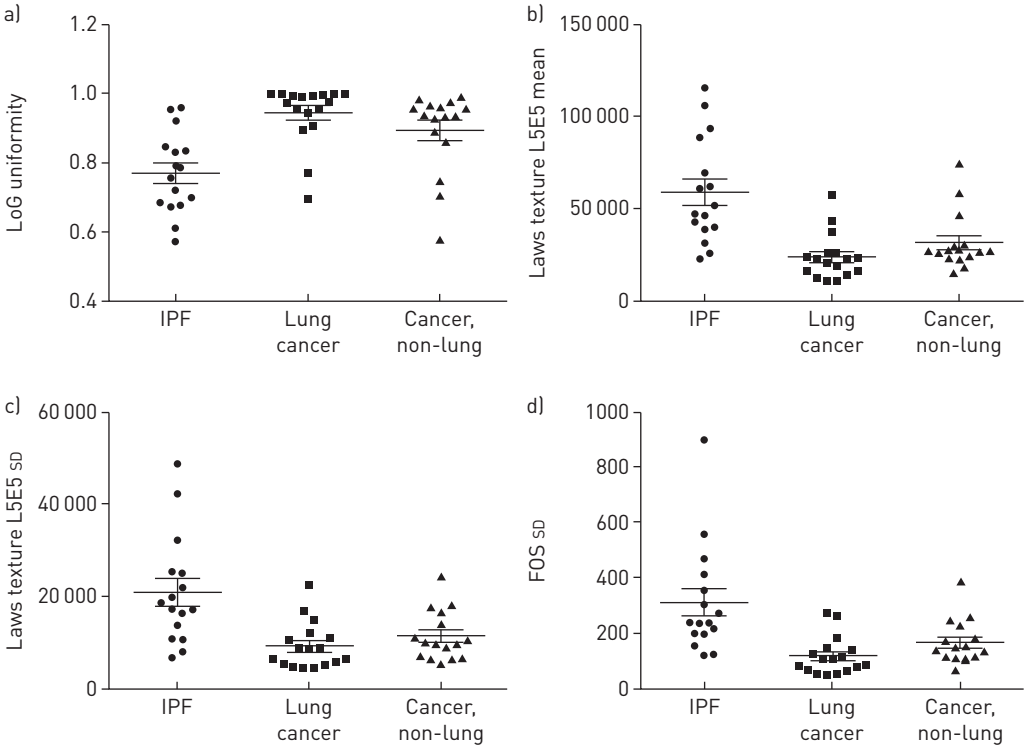

FIGURE 1 Textural analysis of positron emission tomography [^{18}F]-fluorodeoxyglucose signals from normal lung in idiopathic pulmonary fibrosis (IPF) patients and two control groups. Four examples showing significant differences in textural features: a) Laplacian of Gaussian (LoG) uniformity with a 3.84-mm filter (p<0.0001, IPF *versus* pooled controls), b) Laws texture L5E5 mean (p<0.0001), c) Laws texture L5E5 standard deviation (p<0.0001) and d) first order statistics (FOS) standard deviation (p<0.0001).

CT screening studies with "interstitial lung abnormalities". Textural features derived from [^{18}F]-FDG PET are increasingly applied in oncology and tumour heterogeneity is associated with response to therapy [4]. Textural analysis of lung PET-CT imaging is a novel approach that could be used to study early events in IPF pathogenesis, identify early disease, aid prognostication or predict response to therapy.

Shamsuddeen A. Aliyu[1,2], Ged Avery[3], Christopher Cawthorne[2], Stephen J. Archibald[2], Timor Kadir[4], Julien M.Y. Willaime[5], Alyn H. Morice[1], Simon P. Hart[1] and Michael G. Crooks[1]
[1]Respiratory Research Group, Hull York Medical School, Castle Hill Hospital, Cottingham, UK. [2]PET Research Centre, University of Hull, Hull, UK. [3]Hull and East Yorkshire Hospitals NHS Trust, Castle Hill Hospital, Cottingham, UK. [4]Optellum Ltd, Oxford Centre for Innovation, Oxford, UK. [5]Mirada Medical Ltd, Oxford Centre for Innovation, Oxford, UK.

Correspondence: Simon P. Hart, Respiratory Research Group, Hull York Medical School, Castle Hill Hospital, Cottingham, HU16 5JQ, UK. E-mail: s.hart@hull.ac.uk

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