Reply: Measurement of hypoxia in the lung in idiopathic pulmonary fibrosis: a matter of control

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Reply to P-S. Bellaye and co-workers:

We thank P-S. Bellaye and co-workers for their considered and insightful response. Given their finding of [^{18}F]fluoromisonidazole ([^{18}F]F-MISO) uptake in the bleomycin mouse model of fibrosis [1], we too were surprised not to demonstrate a similar signal in patients with idiopathic pulmonary fibrosis (IPF). However, as acknowledged, there are other examples of positron emission tomography (PET) tracers, such as cis-4-[^{18}F]-fluoro-L-proline, yielding PET signals in animal lung fibrosis models that have not been replicated in humans with fibrotic lung disease [2, 3].

PET quantification in the lung, and especially using the [^{18}F]F-MISO ligand, is recognised as particularly challenging, and we adopted methodology proposed in a consensus document from the Society of Nuclear Medicine [4]. P-S. Bellaye and co-workers correctly point out that radiologically normal areas of the lung in IPF may be inappropriate controls if they convey an above background PET signal, as we have shown for [^{18}F]FDG-PET [5]. To investigate this, we measured the uptake of [^{18}F]F-MISO in radiologically normal areas of IPF lung and compared this with radiologically normal lung, distal to the tumour, in several lung cancer patients. We found slightly lower [^{18}F]F-MISO uptake in the normal appearing areas of the IPF patients compared to lung cancer "normal lung" either using full standard PET quantification analysis (pulmonary uptake standardised uptake value (SUV) and tissue-to-blood ratio), including tissue correction [6] or with dynamic acquisition and full kinetic analysis. However, this did not consistently reach statistical significance. Moreover, our irreversible tracer binding parameter, k_5*, showed there was no specific binding of F-MISO in either normal appearing or fibrotic regions of IPF lung. In addition, our dynamic data confirmed that the SUV was virtually the same at 120 min as it was at 220 min, indicating minimal binding of the irreversible F-MISO tracer.

We agree that small studies can generally be hampered by population heterogeneity. Indeed, our own study included patients with mild to severe disease based on lung function, but despite this we found no significant associations between [^{18}F]F-MISO SUV_{mean} and physiological parameters, including forced vital capacity and transfer factor of the lung for carbon monoxide.

Finally, TANGUY *et al.* [1] have demonstrated a dramatic reduction of [^{18}F]F-MISO uptake in response to antifibrotic treatment in pre-clinical models and it has been questioned if this was accounted for in our study. However, our patients were recruited and imaged before such treatments were widely available in the UK national health service (NHS) and only one of our patients was on antifibrotic treatment.

Shareable abstract (@ERSpublications)
***In vivo* PET imaging in IPF patients shows no significant evidence of lung tissue hypoxia**
https://bit.ly/3fywY7K

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Joanna C. Porter[1], Thida Win[2], Kjell Erlandsson[3], Kris Thielemans[3] and Ashley M. Groves[3]

[1]Centre for Inflammation and Tissue Repair, UCL and the UCLH Interstitial Lung Disease Service, London, UK. [2]Respiratory Medicine, Lister Hospital, Stevenage, UK. [3]Institute of Nuclear Medicine, UCL/H, London, UK.

Corresponding author: Joanna C. Porter (joanna.porter@ucl.ac.uk)

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