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

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To the Editor:

We read with great interest the paper by Porter *et al.* [1] published in the October 2021 issue of the *European Respiratory Journal*. The authors' aim was to explore the potential benefit of the hypoxia tracer [^{18}F]fluoromisonidazole ([^{18}F]F-MISO) in idiopathic pulmonary fibrosis (IPF). Given the lack of non-invasive imaging tools for the diagnosis and/or the follow-up of patients with IPF, this study appears to be an essential first step towards the personalised management of IPF patients through imaging biomarkers for early/active fibrosis. *In vivo* molecular imaging, in particular positron emission tomography (PET), has become a crucial tool in preclinical research, clinical trials and medical practice, especially in the field of oncology. In lung fibrosis, recent advances have been made with the aim of developing molecular imaging tools in preclinical models, a necessary step toward clinical certification [2]. Among tracers validated at the preclinical level, imaging probes targeting collagen (^{68}Ga-CBP8 [3]), integrins ([^{18}F]FB-A20FMDV2 [4]) and glucose metabolism ([^{18}F]FDG [5]) have been successfully evaluated in clinical trials and may ultimately improve IPF management.

While chronic hypoxia of the lung is a significant clinical feature in patients with IPF, the study by Porter *et al.* [1] is the first to explore the potential role of the hypoxia tracer [^{18}F]F-MISO in these patients. However, the results of this study were disappointingly far from our expectations considering that high levels of hypoxia biomarkers have been found in IPF patients, suggesting a hypoxic microenvironment in the IPF lung [6]. In addition, our group previously suggested that [^{18}F]F-MISO imaging could be a promising tool for early detection and monitoring in a preclinical model of lung fibrosis [7]. Although we are aware that our preclinical results may not be entirely relevant for human IPF, we believe that the study from Porter *et al.* [1] may suffer from flaws that could explain, at least in part, their underwhelming results. In our opinion, the main issue resides in the use of lung areas with a "normal" appearance as controls for fibrotic areas. When they used this control, Porter *et al.* [1] assumed that the regions of IPF lungs that appear to be normal are *de facto* not hypoxic. We believe that this assumption may be incorrect since we demonstrated in our preclinical results that there was also an increase in [^{18}F]F-MISO lung uptake in areas that seemed "normal" on computed tomography (figure 1). These data are in line with other studies demonstrating that hypoxia inducible transcription factor (HIF)-1α and CA-IX are upregulated, not only in areas of active fibrosis, but also within areas of IPF lungs that appear histologically normal [8]. These findings suggest that the activation of hypoxia signalling is an early event that drives the remodelling of areas in the IPF lung that are not yet fibrotic, thus promoting disease progression. As an alternative, considering that hypoxic volumes are more localised in lung cancer than in IPF, seemingly "normal" zones distant from tumours in lung cancer patients would have been much more reliable controls but would require the inclusion of more than two patients to be statistically relevant. Further, Porter *et al.* [1] do not specify whether the IPF patients included in the work were undertaking anti-fibrotic treatment. This question may be crucial considering that we demonstrated that [^{18}F]F-MISO uptake was dramatically decreased by both nintedanib and pirfenidone in preclinical models [7], and the same effect has been reported in cancer [9].

In addition, while we understand that average pulmonary uptake (SUV_{mean}) values may have been more useful in this study than SUV_{max} (classically used for [^{18}F]F-MISO in oncology) considering that IPF is a diffuse disease, no comparison between SUV_{mean} from IPF and lung tumours is provided. These data

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Despite the discouraging results provided by Porter and co-workers, we believe that there is room for improvements, mainly by using better controls, which may ultimately lead to more promising outcomes for the use of hypoxia-focused imaging in IPF patients https://bit.ly/30Ku2AV

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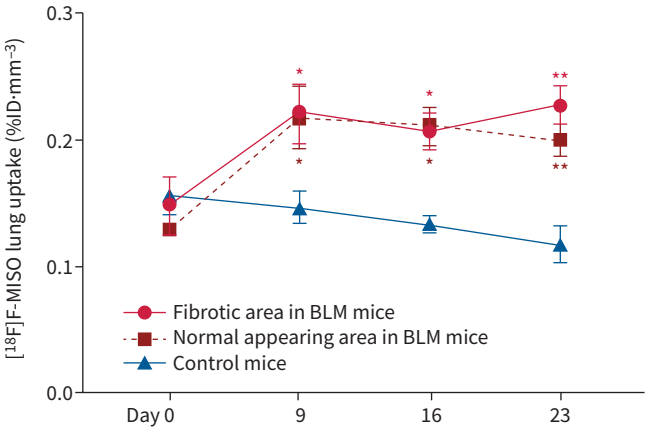

FIGURE 1 Fluorine-18-labelled fluoromisonidazole ([^{18}F]F-MISO) lung uptake is upregulated in seemingly normal and fibrotic lung areas in bleomycin (BLM)-induced lung fibrosis. Graph represents the evolution of [^{18}F]F-MISO lung uptake (% injected dose (ID) per mm^3) in BLM-receiving mice at day 0 (baseline before BLM), and days 9, 16 and 23 in normal appearing and fibrotic lung areas (segmented on computed tomography images). [^{18}F]F-MISO lung uptake in mice receiving NaCl serves as control. Results are presented as mean±SEM. n=5 per group. *: p<0.05; **: p<0.01, for statistical comparison between BLM and control mice. Data from TANGUY *et al.* [7].

could be used to compare the level of hypoxia in tumours and in IPF lungs. Even in hypoxic tumours, [^{18}F]F-MISO uptake can be relatively low (*e.g.* SUV_{mean} between 1.5 and 2 [10]), and one could imagine that the SUV_{mean} presented here (1.6 and 1.55 for control and fibrotic areas, respectively) could mean that both normal appearing and fibrotic lung areas are hypoxic in IPF patients. Therefore, considering the diffuse nature of IPF and the relatively low uptake of [^{18}F]F-MISO, an imaging protocol including a PET scan at 120 min post-injection, which is a common schedule for cancer trials, may have improved SUV values and would have been easier to compare with the existing data in cancer.

While we understand the difficulty of including patients in this type of clinical trial, the heterogeneity of lung function parameters in the IPF cohort may be an additional drawback of the current study. Heterogeneity may be beneficial in a large clinical trial, but it may also hide potentially interesting results in a particular subset of patients (*e.g.* mild *versus* severe fibrosis) in trials with a small number of patients. A correlation between [^{18}F]F-MISO SUV_{mean} and forced vital capacity and/or transfer factor of the lung for carbon monoxide would provide a better idea of whether hypoxia is related to disease stage or severity, as is the case in preclinical models of lung fibrosis [7] and in oncology.

Despite the discouraging results reported by PORTER *et al.* [1], we strongly believe that there is room for improvement, which may ultimately lead to more promising outcomes for the use of hypoxia-focused imaging in IPF patients.

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