Hyperpolarised xenon magnetic resonance spectroscopy for the longitudinal assessment of changes in gas diffusion in IPF

Nicholas D Weatherley,1 Neil J Stewart,1 Ho-Fung Chan,1 Matthew Austin,1,2 Laurie J Smith,1 Guilhem Collier,1 Madhwsha Rao,1 Helen Marshall,1 Graham Norquay,1 Stephen A Renshaw,3 Stephen Mark Bianchi,2 Jim M Wild1

1Polaris, Academic Unit of Radiology, University of Sheffield, Sheffield, UK; 2Academic Directorate of Respiratory Medicine, Sheffield Teaching Hospitals Foundation Trust, Sheffield, UK; 3Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK

ABSTRACT
Prognosticating idiopathic pulmonary fibrosis (IPF) is challenging, in part due to a lack of sensitive biomarkers. A recent article in Thorax described how hyperpolarised xenon magnetic resonance spectroscopy may quantify regional gas exchange in IPF lungs. In a population of patients with IPF, we find that the xenon signal from red blood cells diminishes relative to the tissue/plasma signal over a 12-month time period, even when the diffusion factor for carbon monoxide is static over the same time period. We conclude that hyperpolarised 129Xe MR spectroscopy may be sensitive to short-term changes in interstitial gas diffusion in IPF.

INTRODUCTION
Despite significant developments in our understanding of the pathogenesis of idiopathic pulmonary fibrosis (IPF) and the emergence of efficacious treatments,1,2 prognostication remains challenging. Pulmonary function tests (PFTs), including forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (D LCO), form the basis of assessing progression and treatment response, but are insensitive to longitudinal change.3 An FVC decline of ≥10% is a validated primary endpoint for disease progression and is predictive of mortality,4 but longitudinal data demonstrate substantial inter-patient variability.5 New biomarkers may help to assess disease progression. MRI with hyperpolarised helium (3He) or xenon (129Xe) gas can reveal subtle changes in lung ventilation and microstructure.6 Of particular interest for pulmonary gas exchange assessment is the solubility of xenon in lung parenchyma and blood.6,7 129Xe shows distinct signals from the red blood cells (RBCs) and interstitial tissue/plasma (TP) compartments by virtue of its environment-dependent resonant frequency, which enables evaluation of gas exchange efficiency by MR spectroscopy (MRS). Wang et al recently used 129Xe MRS to identify regions of gas transfer deficit in IPF.8 Herein, we describe preliminary findings evaluating the sensitivity of 129Xe MRS to longitudinal physiological changes in patients with IPF.

METHODS
In a study with National Health Service Research Ethics Committee approval, 18 participants with a multidisciplinary diagnosis of IPF were recruited and provided prospective informed written consent. Five patients were taking antifibrotic treatment on recruitment to the study (four on pirfenidone and one on nintedanib). During the study, a further three patients commenced pirfenidone and two patients commenced nintedanib. All underwent baseline imaging and 10 underwent repeated scans 1–3 hours later. Fourteen participants returned at 6 months (195±24 days) and 13 returned at 12 months (361±31 days). Each underwent pulmonary MRS with hyperpolarised 129Xe gas on a 1.5T whole-body MRI scanner. Scans were well tolerated and completed in all, except one participant at the 12-month visit, who completed neither D LCO, nor the MR breath-hold manoeuvre.

129Xe was polarised under regulatory licence and 600 mL of isotopically enriched xenon was balanced with nitrogen to a total inhaled dose of 1 L. Whole lung 129Xe MRS was performed during a 10–15 s breath-hold after inhaling the gas mixture from functional residual capacity. A pulse-acquire sequence was used to acquire whole-lung spectra of 129Xe in the TP and RBC compartments (bandwidth: 1.8 kHz; flip angle: 90°; repetition time: 1 s). Data analysis was performed using MATLAB. After discarding the first spectrum, spectra were averaged and zeroth-order phase corrected, and integrals over the RBC and TP spectral peaks were evaluated to derive the ratio RBC/TP.

PFTs were performed on the same day as MR. Spearman’s r determined the strength of correlations. Friedman tests evaluated the significance of differences in baseline, 6 and 12-month metrics. Intraclass correlation coefficient and Bland-Altman analyses assessed reproducibility of RBC/TP.

Two-tailed p values of <0.05 determined statistical significance.

RESULTS
Summary statistics of demographics, PFTs and RBC/TP measurements (median [IQR]) are as follows: age (years) 71.5 (67.8–74.3); FVC (%-predicted) 75.1 (64.3–95.1); D LCO (%-predicted) 42.0 (34.6–56.3); baseline RBC/TP 0.26 (0.18–0.34). Same-day repeat scanning yielded highly reproducible intrapatient RBC/TP ratios, (see Bland-Altman plot, figure 1; intraclass correlation 0.963). A statistically significant correlation (r; 95%CI) was observed between baseline RBC/TP and D LCO (r=0.677; 0.293 to 0.873), but not FVC (r=0.336; –0.170 to 0.702). Correlations with D LCO (%-predicted) remained significant at...
DISCUSSION

Hyperpolarised $^{129}$Xe MRS is highly reproducible and sensitive to longitudinal changes in pulmonary gas exchange efficiency in IPF. The correlation between RBC:TP and $D_{LCO}$ suggests the techniques reflect similar underlying gas exchange pathophysiology, although with gases that have different membrane diffusion properties. While $D_{LCO}$ showed no longitudinal change, RBC:TP demonstrated a trend to decline over 6 months and a statistically significant decline over 12 months. Our baseline RBC:TP and $D_{LCO}$ correlation is slightly weaker than reported in others possibly due to differences in MRS parameters, reference equations for $D_{LCO}$, or inclusion of healthy volunteer data in previous correlations.

$D_{LCO}$ is calculated from exhaled gas concentrations measured at the mouth, while MRS obtains $^{129}$Xe measurements directly from the alveoli, alveolar-capillary membrane and RBCs. The observed reduction in RBC:TP when $D_{LCO}$ is stable may therefore result from differing gas properties and measurement procedure, reflecting different pathophysiology. These differences may be emphasised by the postures used when measuring $D_{LCO}$ (sitting) and $^{129}$Xe RBC:TP (supine). The supine posture may cause a partial redistribution of ventilation and perfusion to regions of the lung less affected by disease. Indeed, Wang et al demonstrated how TP signal increases and RBC signal falls in lung tissue afflicted with IPF and how RBC signal is almost absent in areas severely afflicted. The $^{129}$Xe signal from the tissue and RBC compartments is weighted by a combination of specific ventilation, interstitial thickening, delayed gas diffusion and perfusion deficit. In future $^{129}$Xe spectroscopic studies, additional measurement the $^{129}$Xe alveolar gas signal as a reference, alongside contrast enhanced perfusion MRI may provide complementary physiological information to help understand the observed RBC:TP decline. Additionally, acquisition of longitudinal CT data could yield insight into the mechanism of...
RBC:TP change. We also note that inflation level may influence RBC:TP ratio in a non-negligible manner. Thus, future studies should consider varying the inhaled xenon gas dose with lung capacity.

Despite relatively limited participant numbers, we were able to identify a statistically significant decline in RBC:TP, indicating the power of this approach. The observed FVC decline is small, but consistent with treatment intervention studies and suggests a clinically significant decline in lung function and parallel gas exchange impairment. The decline observed in MRS-derived RBC:TP is underpinned by different pathophysiological mechanisms to that in FVC, and thus, RBC:TP may be additive to our current repertoire of physiological assessment tools. With further development, this technique may offer a sensitive endpoint for early-stage clinical trials.

Correction notice This article has been corrected since it was published Online First. The copyright licence was changed from CC BY-NC to CC-BY.

Acknowledgements The authors would like to thank all members of the POLARIS group. In particular, Leanne Armstrong and Jennifer Rodgers for administrative support.

Contributors Conception and design: NDW, NJS, SAR, SMB and JMW. MRI experiments: NDW, NJS, H-FC, GN, JMW, GC, MR and HM. Postprocessing and statistical analysis: NDW and NJS. Pulmonary function tests: MA and LJS. Manuscript drafting for intellectual content: All authors. Manuscript editing: All authors.

Funding Funding for this study was provided by National Institute for Health Research; Grant number: NIHR- RP-R3-12-027 and Medical Research Council; Grant number: MR/M008894/1.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Liverpool Central NHS REC.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES