Functional xenon-129 magnetic resonance imaging response to antifibrotic treatment in idiopathic pulmonary fibrosis

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To the Editor:

Progression of idiopathic pulmonary fibrosis (IPF) is highly variable [1] and it is clinically challenging to effectively manage care and tailor treatment regimens using antifibrotic medications, such as nintedanib and pirfenidone, on a patient-specific basis [2]. Clinical evaluation of the functional response to these treatments is limited largely to pulmonary function tests (PFTs) (*e.g.* forced vital capacity (FVC), percentage predicted forced expiratory volume in 1 s (FEV_1), diffusing capacity of the lung for carbon monoxide (D_{LCO}) [3] and/or progression-free survival [4]). The development of more sensitive biomarkers that can provide longitudinal evaluation of regional treatment response would have meaningful clinical utility. Hyperpolarised (HP) xenon-129 (^{129}Xe) magnetic resonance imaging (MRI) has shown potential for evaluating both regional ventilation and gas exchange, with a strong focus on applications in IPF [5–7]. Specifically, HP ^{129}Xe MRI spectroscopy measures of red blood cell (RBC) ^{129}Xe uptake across the lung tissue and plasma barrier (hereafter "membrane") from the alveolar space, called the RBC-to-membrane ratio, has been shown to be a possible biomarker of future IPF disease progression [8].

In this work, we investigate our hypothesis that IPF patients treated with antifibrotic medications will show improved longitudinal trajectories in this candidate biomarker over the course of 1 year. These results have been introduced previously in abstract form [9]. The study was Health Insurance Portability and Accountability Act compliant and informed consent was obtained in accordance with approved institutional review board (UW IRB 2013-0266 and UW IRB 2014-1572) and investigational new drug (United States Food and Drug Administration IND# 118077) protocols. 25 participants with IPF were recruited prospectively, 21 of whom (19 males, mean±SD age 70.1±8.5 years) underwent HP ^{129}Xe MRI ventilation and spectroscopic imaging at baseline and at 1-year follow-up. Criteria for study inclusion were outpatients aged >18 years with clinical diagnosis of IPF by established means. Potential participants were excluded for any of the following reasons: respiratory illness within 30 days of MRI; oxygen saturation on room air <90%; history of ventricular cardiac arrhythmia; cardiac arrest within the past year; pregnancy; or unable to maintain 15-s breath-hold. All 21 participants underwent treatment for IPF according to the standard of care such that a subgroup was treated with antifibrotic medication ("antifibrotic" group; n=12, 11 males, age 68.1±7.7 years), while the remaining patients were treated with alternative therapies ("no-antifibrotic" group; n=9, eight males, age 72.8±9.2 years). Participants were considered part of the antifibrotic group if they received antifibrotic medication at any point during the study (pirfenidone: n=8 for full year, n=2 for part of year; nintedanib: n=1 for full year, n=1 for part of year). Patients receiving only partial treatment were medicated as follows: two were treated at baseline, but stopped antifibrotic treatment before 1 year (one after 3 months; one after 6 months), while one patient began antifibrotic treatment 9 months after baseline. Potential comorbidities in this population include history of smoking (n=10), COPD (n=1), emphysema (n=1), coronary artery disease (n=7) and hypertension (n=8). PFT measurements (single-breath method) of FEV_1 % pred and FVC % pred by spirometry and D_{LCO} % pred were obtained immediately prior to imaging. Percentage predicted values for PFT measures were calculated based on reference values of the Global Lung Function Initiative [10].

Ventilation and gas-exchange HP ^{129}Xe MRI were acquired and processed according to previously described protocols [11, 12]. Gas-exchange spectropic MRI was decomposed into images of HP ^{129}Xe residing in the RBCs, lung tissues and plasma (membrane) and airspaces (gas), then converted to the ratios

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A measure of regional gas exchange on HP ^{129}Xe MRI was able to detect apparent improvements in IPF patients treated with antifibrotic medication after 1 year, while no such improvements were found in patients treated with conventional therapies https://bit.ly/3ZXipzD

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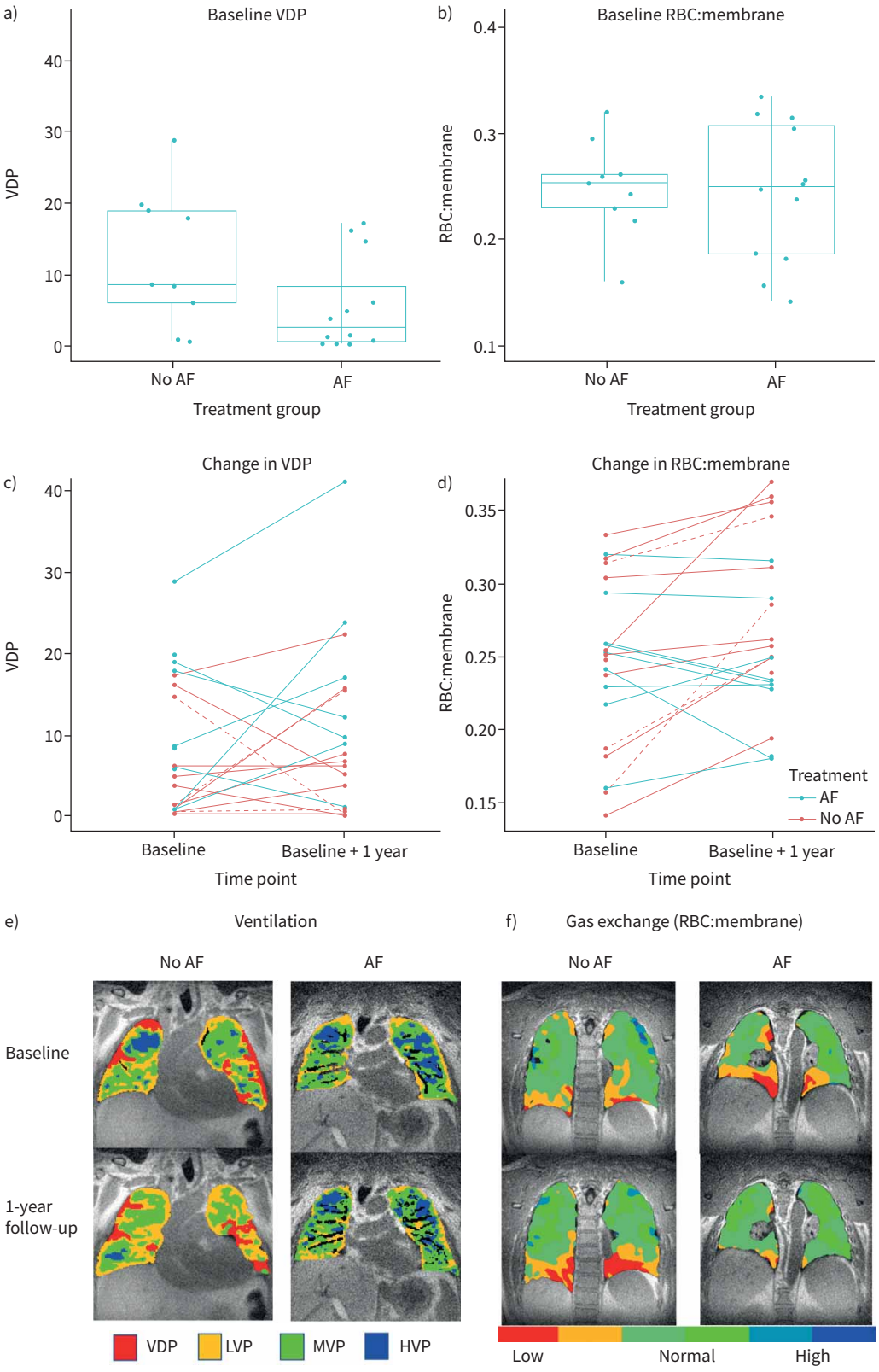

FIGURE 1 Plots of a and b) baseline and c and d) change in b and d) red blood cell (RBC)-to-membrane ratio and a and c) ventilation defect percentage (VDP). RBC-to-membrane ratio significantly improved in the antifibrotic (AF) group over 1 year (p=0.002) and increased over that time in 11 out of 12 patients receiving antifibrotic medication. Also shown are images of f) RBC-to-membrane ratio and e) ventilation from an idiopathic pulmonary fibrosis (IPF) patient not taking antifibrotic medication (no-AF) (male, age 65 years) and

an IPF patient treated with antifibrotics (male, age 60 years) at baseline and after 1 year. e) VDP is higher in the no-AF case relative to the patient treated with antifibrotic medication. f) RBC-to-membrane ratio appears to decrease over time in the no-AF patient, and recovers in the patient taking antifibrotics. LVP: low ventilation percentage; MVP: medium ventilation percentage; HVP: high ventilation percentage.

of RBC:gas, membrane:gas and RBC:membrane for analysis. Voxel-wise ventilation within the lung was automatically classified into four ventilation metrics: ventilation defect percentage (VDP), low ventilation percentage, medium ventilation percentage and high ventilation percentage, where percentage refers to the percentage of total lung volume containing each classification. Statistical comparisons across groups are made using the Wilcoxon rank-sum tests (unpaired), and comparisons across time (within individuals of each group) are made using the Wilcoxon signed-rank tests (paired).

Baseline disease was more severe, by certain measures, in the antifibrotic group (lower D_{LCO}: no-antifibrotic mean±SD 68±14% pred, antifibrotic 52±8.4% pred, p=0.025; and tending to lower FVC: no-antifibrotic 89±16% pred, antifibrotic 76±17% pred, p=0.070). However, no significant difference in gender–age–physiology score was found between groups at baseline (no-antifibrotic 3±1, antifibrotic 3.5 ±0.7; p=0.16). For imaging measures at baseline, the RBC-to-membrane ratio was comparable in both groups (no-antifibrotic 0.248±0.045, antifibrotic 0.245±0.066; p=0.86) (figure 1a and b). By 1 year, D_{LCO} (no-antifibrotic 63±19% pred, antifibrotic 51±11% pred; p=0.21) and FVC (no-antifibrotic 88±15% pred, antifibrotic 73±19% pred; p=0.11) were statistically equivalent, and there were no changes in PFT measures within each patient between baseline and 1 year in either treatment group (D_{LCO}: no-antifibrotic −3.7±7.1% pred, p=0.25; antifibrotic 0.8±6.7% pred, p=0.63; FVC: no-antifibrotic −1.5±3.3% pred, p=0.27; antifibrotic −3.0±11.5% pred, p=1).

The RBC-to-membrane measure of gas exchange showed an absolute improvement within each patient after 1 year in the antifibrotic group (ΔRBC:membrane 0.046±0.042, p=0.001) and did not change in the no-antifibrotic group (ΔRBC:membrane −0.010±0.028, p=0.30) (figure 1d). Consistent with individual improvement in gas exchange compared to baseline, the RBC:membrane for the antifibrotic group increased on a per-patient basis compared to no-antifibrotic treatment (p=0.002). For ventilation on MRI, no significant changes within each patient were observed for VDP within the antifibrotic group (ΔVDP 1.4 ±8.7, p=0.38) (figure 1c). Overall, change in VDP within individual patients over 1 year was comparable between treatment groups (p=0.46). Regional maps of these HP ^{129}Xe measurements from representative subjects are provided in figure 1e and f.

A notable finding was that D_{LCO} did not respond to treatment, while RBC-to-membrane ratio did, despite previous work demonstrating a strong association between D_{LCO} and RBC-to-membrane ratio in healthy and IPF patients and similar reported variability in the repeatability of each measurement [13]. This finding suggests improved sensitivity to treatment response from regional data provided by HP ^{129}Xe MRI *versus* the global changes reported by D_{LCO} % pred. The physiological basis for the improvement in RBC-to-membrane ratio in the antifibrotic treatment group is unclear. There could be preservation of vascular reserve that enables more robust response to the disease process, and/or suspension of structural remodelling leading to more efficient gas-diffusion across the alveolar–capillary membrane. It is worth noting that ventilation defects did not respond to treatment, despite differing slightly between the treatment groups at baseline, with the no-antifibrotic group showing more ventilation abnormalities. It is possible that ventilation differences were driven by comorbid obstructive disease that is minimally affected by antifibrotic treatments.

There were limitations to this study. The small sample size and baseline differences in the disease severity of the antifibrotic *versus* no-antifibrotic groups are important limitations. However, it is worth noting that baseline severity was greater in the antifibrotic group, possibly resulting in a larger potential for improvement irrespective of treatment regimen. This seems unlikely to fully explain the observed results, given that IPF lung disease typically stabilises or progresses under non-antifibrotic therapy [1]. The fact that three patients were only treated for part of the year with antifibrotic medication is a further limitation of this work. It is difficult to determine the effect this might have and could potentially have a meaningful influence on these findings. Finally, the presence of comorbidities in this cohort could influence the interpretation of these findings as well. While no clinical record of pulmonary hypertension (which can affect gas exchange measures) was noted, specific investigations were not made to rule out its presence. Additionally, the high incidence of smoking could be associated with emphysema without physiological obstruction, again potentially influencing these results.

In conclusion, a regional HP ^{129}Xe MRI biomarker of gas exchange improved in IPF patients undergoing antifibrotic therapy compared to those on alternative therapies, while clinical PFT measures did not. The RBC-to-membrane ratio, a regional measure of gas-exchange efficiency, improved significantly after 1 year in patients undergoing antifibrotic treatment, suggesting promise as a biomarker of early-stage response. Larger prospective studies investigating ventilation, perfusion and gas exchange in IPF progression and treatment are needed.

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