



## Early View

Research letter

# “Functional $^{129}\text{Xe}$ MRI Response to Antifibrotic Treatment in Idiopathic Pulmonary Fibrosis”

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**Title:** “Functional  $^{129}\text{Xe}$  MRI Response to Antifibrotic Treatment in Idiopathic Pulmonary Fibrosis”

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**Take Home Message:** A measure of regional gas exchange on HP  $^{129}\text{Xe}$  MRI was able to detect apparent improvements in IPF patients treated with anti-fibrotic medication after 1 year, while no such improvements were found in patients treated with conventional therapies.

Progression of Idiopathic pulmonary fibrosis (IPF) is highly variable<sup>1</sup> and it is clinically challenging to effectively manage care and tailor treatment regimens using antifibrotic medications, such as nintedanib<sup>™</sup> and pirfenidone<sup>™</sup>, on a patient-specific basis<sup>2</sup>. Clinical evaluation of the functional response to these treatments is limited largely to pulmonary function tests (PFTs) (e.g. forced vital capacity (FVC), Forced expiratory volume in one minute percent predicted (FEV1%), diffusion-lung carbon monoxide (DLCO)<sup>3</sup> and/or progression free survival<sup>4</sup>). The development of more sensitive biomarkers that can provide longitudinal evaluation of regional treatment response would have meaningful clinical utility. Hyperpolarized (HP) xenon-129 (<sup>129</sup>Xe) MRI has shown potential for evaluating both regional ventilation and gas exchange, with a strong focus on applications in IPF<sup>5-7</sup>. Specifically, HP <sup>129</sup>Xe MRI spectroscopy measures of red blood cell (RBC) <sup>129</sup>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<sup>8</sup>.

In this work, we investigate our hypothesis that IPF patients treated with anti-fibrotic 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<sup>9</sup>. The study was HIPAA 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 (FDA IND# 118077) protocols. A total of 25 participants with IPF were recruited prospectively, 21 of which (19 male, ages 70.1±8.5 years) underwent HP <sup>129</sup>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 second breath hold. All 21 participants underwent treatment for IPF according to the standard of care such that a subgroup was treated with anti-fibrotic medication (“AF” group; N=12, 11 male, ages  $68.1 \pm 7.7$  years), while the remaining patients were treated with alternative therapies (“no-AF” group; N=9, 8 male, ages  $72.8 \pm 9.2$  years). Participants were considered part of the AF group if they received anti-fibrotic 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: 2 were treated at baseline but stopped AF treatment before 1-year (1 after 3 months, 1 after 6 months), while 1 began AF 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). Pulmonary function test (PFT) measurements (single-breath method) of FEV<sub>1</sub>%<sub>p</sub> and FVC%<sub>p</sub> by spirometry and DLCO%<sub>p</sub> were obtained immediately prior to imaging. Percent predicted (%p) values for PFT measures were calculated based on reference values of global lung function initiative (GLI)<sup>10</sup>.

Ventilation and Gas-exchange HP <sup>129</sup>Xe MRI were acquired and processed according to previously described protocols<sup>11,12</sup>. Gas-exchange spectropic MRI was decomposed into images of HP <sup>129</sup>Xe residing in the red blood cells (RBC), lung tissues and plasma (Membrane) and airspaces (Gas), then converted to the ratios of RBC:Gas,

Membrane:Gas and RBC:Membrane for analysis. Voxel-wise ventilation within the lung was automatically classified into 4 ventilation metrics: ventilation defect percent (VDP), low ventilation percent (LVP), medium ventilation percent (MVP) and high ventilation percent (HVP), where percent refers to the percent 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 AF group (lower DLCO<sub>%p</sub>, no-AF: 68±14, AF: 52±8.4;  $P=0.025$  and tending to lower FVC<sub>%p</sub>, no-AF: 89±16, AF: 76±17;  $P=0.070$ ). However, no significant difference in GAP score was found between groups at baseline, (no-AF: 3±1, AF: 3.5±0.7;  $P=0.16$ ). For imaging measures at baseline, the RBC:Membrane was comparable in both groups (no-AF: 0.248±0.045, AF: 0.245±0.066,  $P=0.86$ ) (**Fig. 1a,b**). By 1 year, the DLCO<sub>%p</sub> (no-AF: 63±19, AF: 51±11;  $P=0.21$ ) and FVC<sub>%p</sub> (no-AF: 88±15, AF: 73±19,  $P=0.11$ ) were statistically equivalent, and there were no changes in PFT measures *within each patient* between baseline and 1 year in either treatment group (DLCO<sub>%p</sub>, no-AF: -3.7±7.1,  $P=0.25$ ; AF: 0.8±6.7,  $P=0.63$ ; FVC<sub>%p</sub>, no-AF: -1.5±3.3,  $P=0.27$ ; AF: -3.0±11.5,  $P=1$ ).

The RBC:Membrane measure of gas exchange showed an absolute improvement within each patient after 1 year in the AF group ( $\Delta$ RBC:Membrane = .046±.042,  $P=.001$ ) and did not change in the no-AF group ( $\Delta$ RBC:Membrane = -.010±.028,  $P=.30$ ) (**Figure 1d**). Consistent with individual improvement in gas exchange compared to baseline, the RBC:Membrane for the AF group increased on a per patient basis compared to no-AF treatment ( $P=0.002$ ). For ventilation on MRI, no

significant changes within each patient were observed for VDP within the AF group ( $\Delta\text{VDP}=1.4\pm 8.7$ ,  $P=0.38$ ) (**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  $^{129}\text{Xe}$  measure from representative subjects are provided in **Figure 1e,f**.

A notable finding was that DLCO did not respond to treatment, while RBC:Membrane did, despite previous work demonstrating a strong association between DLCO and RBC:Membrane in healthy and IPF patients and similar reported variability in the repeatability of each measurement<sup>13</sup>. This finding suggests improved sensitivity to treatment response from regional data provided by HP  $^{129}\text{Xe}$  MRI versus the global changes reported by DLCO<sub>%p</sub>. The physiologic basis for the improvement in RBC:Membrane in the AF treatment group is yet unclear. There could be preservation of vascular reserve that enables more robust response to the disease process, and/or suspension of structural remodeling 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-AF group showing more ventilation abnormalities. It is possible that ventilation differences were driven by comorbid obstructive disease that is minimally affected by anti-fibrotic treatments.

There were limitations to this study. The small sample size and baseline differences in the disease severity of the AF vs. no-AF groups are important limitations. However, it is worth noting that baseline severity was greater in the AF 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

stabilizes or progresses under non-antifibrotic therapy<sup>1</sup>. The fact that 3 patients were only treated for part of the year with anti-fibrotic 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 physiologic obstruction, again potentially influencing these results.

In conclusion, a regional HP <sup>129</sup>Xe MRI biomarker of gas-exchange improved in IPF patients undergoing anti-fibrotic therapy compared to those on alternative therapies, while clinical PFT measures did not. The RBC:Membrane ratio, a regional measure of gas-exchange efficiency, improved significantly after one 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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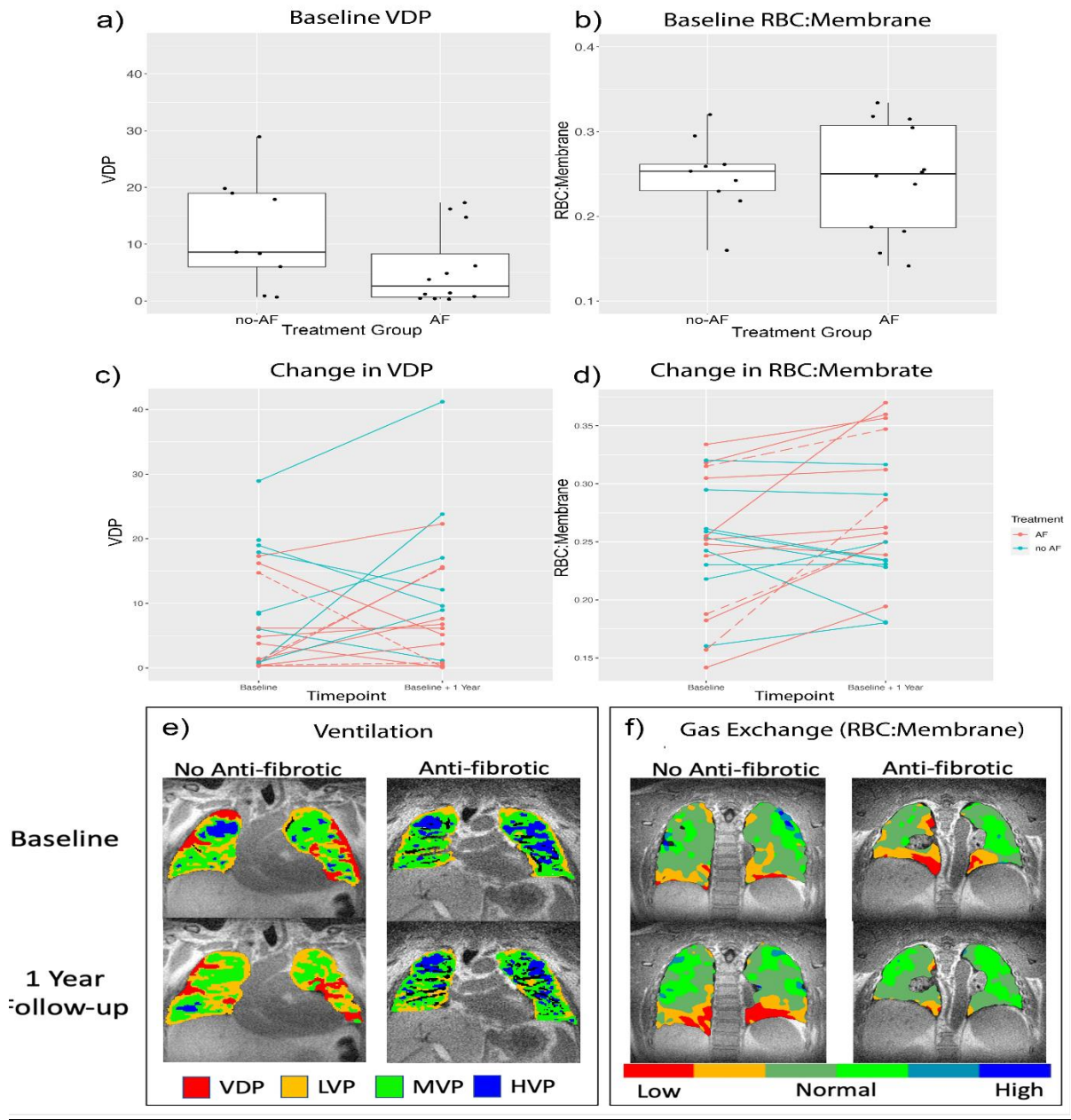


Figure 1. Plots of change (a,b) and baseline (e,f) in RBC:Membrane (a,e) and VDP (b,f). RBC:Membrane significantly improved in the AF group over 1 year ( $P=.002$ ) and increased over that time in 11 out of 12 patients receiving antifibrotic medication. Also shown are images of RBC:Membrane ratio (c) and ventilation (d) from an IPF patient not taking antifibrotic medication (male, age 65) and an IPF patient treated with antifibrotics (male, age 60) at baseline and after 1 year. RBC:Membrane appears to decrease over time in the no-antifibrotic patient (c, left), and recover in the patient taking antifibrotics (d, right). VDP is higher in the no-antifibrotic case (d, left) relative to the patient treated with antifibrotic medication (d, right).