ORIGINAL ARTICLE

Using hyperpolarized $^{129}$Xe MRI to quantify regional gas transfer in idiopathic pulmonary fibrosis

Jennifer M Wang,1 Scott H Robertson,2,3 Ziyi Wang,2,4 Mu He,2,5 Rohan S Virgincar,2,4 Geoffrey M Schrank,2 Rose Marie Smigla,6 Thomas G O’Riordan,7 John Sundy,7 Lukas Ebner,8,9 Craig R Rackley,6 Page McAdams,9 Bastiaan Driehuys2,3,4,9

ABSTRACT

Background Assessing functional impairment, therapeutic response and disease progression in patients with idiopathic pulmonary fibrosis (IPF) continues to be challenging. Hyperpolarized $^{129}$Xe MRI can address this gap through its unique capacity to image gas transfer three-dimensionally from airspaces to interstitial barrier tissues to red blood cells (RBCs). This must be validated by testing the degree to which it correlates with pulmonary function tests (PFTs) and CT scores, and its spatial distribution reflects known physiology and patterns of disease.

Methods 13 healthy individuals (33.6±15.7 years) and 12 patients with IPF (66.0±6.4 years) underwent $^{129}$Xe MRI to generate three-dimensional quantitative maps depicting the $^{129}$Xe ventilation distribution, its uptake in interstitial barrier tissues and its transfer to RBCs. For each map, mean values were correlated with PFTs and CT fibrosis scores, and their patterns were tested for the ability to depict functional gravitational gradients in healthy lung and to detect the known basal and peripheral predominance of disease in IPF.

Results $^{129}$Xe MRI depicted functional impairment in patients with IPF, whose mean barrier uptake increased by 188% compared with the healthy reference population. $^{129}$Xe MRI metrics correlated poorly and insignificantly with CT fibrosis scores but strongly with PFTs. Barrier uptake and RBC transfer both correlated significantly and with diffusing capacity of the lungs for carbon monoxide ($r=0.75$, $p<0.01$) and $r=0.72$, $p<0.01$), while their ratio (RBC/barrier) correlated most strongly ($r=0.94$, $p<0.01$). RBC transfer exhibited significant anterior-posterior gravitational gradients in healthy volunteers, but not in IPF, where it was significantly impaired in the basal ($p<0.02$) and subpleural ($p<0.01$) lung.

Conclusions Hyperpolarized $^{129}$Xe MRI is a rapid and well-tolerated exam that provides region-specific quantification of interstitial barrier thickness and RBC transfer efficiency. With further development, it could become a robust tool for measuring disease progression and therapeutic response in patients with IPF, sensitively and non-invasively.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF), the most common interstitial pneumonia, is a devastating disease with a poor prognosis and estimated survival of 2–3 years after diagnosis.1,2 Historically, treatment has been limited to lung transplantation.3,4 but today, patients are routinely treated with antifibrotic therapy using either the tyrosine kinase inhibitor, nintedanib, or the tumour growth factor-beta inhibitor, pirfenidone.5,6 However, treatment of IPF and development of new therapies continue to be hampered by the lack of reliable metrics to assess therapeutic response and disease progression. To date, the primary indicators have been forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO).7 While DLCO measures gas exchange, it has been difficult to standardise in multi-institutional trials.7 Thus, FVC is used as a surrogate endpoint in most clinical trials, despite the continued lack of consensus on a threshold to define clinically significant decline, predict outcomes and validate treatment decisions.1,5,6,8–10

The pathogenesis of IPF is thought to involve excess collagen deposition that limits the capacity of alveoli to participate in gas exchange.4 However, the disease is heterogeneous in its distribution, and this cannot be captured using global metrics. Thus, imaging is needed to highlight and quantify disease activity regionally. To this end, high-resolution CT has become a mainstay in IPF, detecting fibrotic...
Established metrics and to characterise the spatial distribution at 0 ppm, 198 ppm and 217 ppm corresponding to 129Xe in airspaces, evidence that in IPF 129Xe uptake in the barrier tissues is also cells (RBCs). Moreover, in each of these compartments, 129Xe exhibits distinct resonance frequency shifts\(^{16,17}\) (figure 1).

Figure 1  (A) Diagram of gas-phase 129Xe transfer from alveoli to interstitial barrier tissues and capillary RBCs that comprise the dissolved phased signal. (B) The 129Xe spectrum exhibits three resonances in lung at 0 ppm, 198 ppm and 217 ppm corresponding to 129Xe in airspaces, dissolved in barrier and RBCs.

Changes and structural abnormalities to establish the presence of a usual interstitial pneumonia (UIP) pattern without the need for surgical lung biopsies.\(^1\) This has led to further interest in using quantitative CT to measure longitudinal change, assess disease severity and predict mortality.\(^{11–13}\) However, the structural alterations detected on CT often do not correlate well with patient symptoms.\(^14\)

A promising modality by which to assess regional function is MRI using inhaled hyperpolarized (HP) 129Xe gas. This method is rapid, well tolerated\(^15\) and allows for gas uptake and transfer to be assessed in a spatially resolved manner. On inhalation, xenon diffuses from the alveoli, through pulmonary barrier tissues comprised of alveolar epithelial cells, interstitial tissues, capillary endothelial cells, and plasma, and finally into capillary red blood cells (RBCs). Moreover, in each of these compartments, 129Xe exhibits distinct resonance frequency shifts\(^{16,17}\) (figure 1A,B) that enable its uptake in them to be measured separately.\(^18–22\)

Previously, whole-lung spectroscopic measurements demonstrated that the ratio of 129Xe uptake in RBCs versus barrier was dramatically reduced in subjects with IPF compared with healthy volunteers.\(^17\) This work was subsequently extended to produce isotropic three-dimensional (3D) images of 129Xe in the airspaces, barrier and RBCs and qualitatively revealed that RBC distribution derived from a healthy cohort.\(^31\) The barrier and RBC compartments with 6.3 mm isotropic voxels.

Image acquisition and reconstruction

129Xe gas transfer MRI was acquired on a 1.5T scanner (GE EXCITE 15M4), using an interleaved radial acquisition of gas-phase and dissolved-phase images during a 15s breath-hold.\(^39\) Images were acquired at an echo time (TE,\(^{19}\)) of 0.9 ms that allows the barrier and RBC signals to be separated by the 1-point Dixon method.\(^21\) This generated separate isotropic 3D images of the gas, barrier and RBC compartments with 6.3 mm isotropic voxels.

Image processing and analysis

The gas-phase images were rendered into quantitative maps by rescaling by their top percentile of intensities and assigning each voxel into one of six colour clusters. These clusters each span an intensity range equal to one SD of the ventilation reference distribution derived from a healthy cohort.\(^34\) The barrier and RBC images were divided on a voxel-by-voxel basis by the gas-phase intensities to create maps of barrier uptake and RBC transfer. These methods were dramatically reduced in subjects with IPF compared with healthy volunteers.\(^17\) This work was subsequently extended to produce isotropic three-dimensional (3D) images of 129Xe in the airspaces, barrier and RBCs and qualitatively revealed that RBC distribution derived from a healthy cohort.\(^31\) The barrier and RBC compartments with 6.3 mm isotropic voxels.
Functional gradient analysis

To test the validity of the spatial distribution in functional gas transfer MRI, signal gradients were quantified in three directions. First, the lungs were divided into two equal volumes in the anterior/posterior direction to test the hypothesis that gravitational effects that increase tissue density and perfusion to the dependent lung in healthy subjects would be eliminated in IPF. Similarly, gradients were calculated in the apical/basal direction to assess the hypothesis that impaired function in IPF would show a basal predominance,26 and finally gradients in the central/peripheral direction were calculated to test the hypothesis that impaired function would also follow a peripheral predominance.27 This was done by defining the peripheral lung as the outermost 2–3 cm of the subpleural lung perimeter. All spatial gradients were calculated by dividing the mean signal difference between regions by their average.

Statistical methods

All statistical analyses were performed using JMP 12 (SAS Institute, Cary, North Carolina, USA). The unpaired two-tailed Student’s t-test was used to evaluate differences in the spatial distribution of gas transfer. Linear regression analysis and the Pearson correlation coefficient (r) were used to assess correlation between functional MRI metrics and CT fibrosis scores, as well as PFT results. For all comparisons, the level of significance was 5% (p<0.05).

RESULTS

Single-breath, isotropic images of gas and dissolved-phase 129Xe were successfully acquired in all subjects and reliably decomposed into separate ventilation, barrier uptake and RBC transfer maps. Subject demographics, PFT results and functional imaging-derived ratios are summarised in table 1.

Representative gas transfer maps in healthy subjects versus subjects with IPF

Representative ventilation, gas transfer maps and CT images are depicted in figure 2A for a healthy control subject (FVC=97% predicted, DLco=113% predicted). All maps consist largely of green voxels that represent ratios falling within ±1 standard deviation of the reference healthy mean. While all maps exhibited mean values close to the reference mean (ventilation=93%, barrier=120%, RBC=121%), they do exhibit notable gradients as both barrier uptake and RBC transfer increase towards the gravitationally dependent lung. However, only a modest percentage of voxels fell into BarrierHigh (0.5%) and RBCLow (10%). Low RBC transfer was seen primarily in the anterior, non-gravitationally dependent lung. This pattern of few pixels falling in BarrierHigh and RBCLow was generally found to exist in the healthy cohort as shown in table 1.

Figure 2B depicts 129Xe functional maps in a subject with moderate IPF (FVC=55% predicted, DLco=31% predicted, CT fibrosis score=25.4%). Although ventilation (mean=91%) was not significantly different from the healthy volunteer, the barrier signal was strikingly enhanced throughout the lung (206% of reference), with 74% of voxels falling in BarrierHigh. Enhanced barrier uptake was most notable in the subpleural regions, which was accompanied by reduced RBC transfer (57% of reference), with 52% falling into RBCLow. The corresponding CT images depict predominantly basal and peripheral reticulation and areas of ground glass attenuation, with mild traction bronchiectasis in the affected areas.

Figure 2C depicts ventilation and gas transfer maps in a patient with severe IPF (FVC=42% predicted, DLco=23% predicted, CT fibrosis score=34.2%). Ventilation maps have a reduced mean (83% of reference), but the most striking feature is the highly elevated barrier uptake throughout most of the lung (200% of reference, BarrierHigh=65%). Similarly, this subject exhibited significant regions of low RBC transfer (49% of reference and RBCLow=65%). Low RBC transfer was most evident in the posterior and basilar lung. These matched well with extensive distortion of the lung architecture and honeycombing seen on CT. Interestingly, in portions of these posterior slices, the barrier uptake was in the normal range.

Figure 2D shows ventilation and gas transfer maps in another IPF subject with severe disease (FVC=62% predicted,
Interstitial lung disease

Correlation with pulmonary function tests

Almost all image-derived average gas transfer metrics, ventilation, barrier uptake, RBC transfer and RBC/barrier ratio, correlated significantly with FVC and DL\textsubscript{CO} (figure 3); the only exception was between ventilation and DL\textsubscript{CO}. Ventilation correlated moderately and positively with FVC (r=0.39, p=0.04) but not significantly with DL\textsubscript{CO} (r=0.35, p=0.06). Barrier uptake correlated negatively and significantly with both FVC (r=-0.61, p<0.01) and DL\textsubscript{CO} (r=-0.75, p<0.01). RBC transfer correlated positively and significantly with both FVC (r=0.63, p<0.01) and DL\textsubscript{CO} (r=0.72, p<0.01). Overall, the strongest correlation was between RBC/barrier ratio and DL\textsubscript{CO} (r=0.94, p<0.01).

Spatial patterns of gas transfer

Although 129Xe gas transfer metrics did not correlate with structural CT scores, spatial gradients in 129Xe gas transfer followed expected patterns (figure 4). Ventilation maps in both cohorts demonstrated increasing intensity from the anterior to posterior and apical to basal directions but decreasing intensity from the central to peripheral direction. However, none of these gradients were significantly different between healthy subjects and subjects with IPF. Notably,
barrier uptake exhibited a significantly stronger anterior to posterior gradient in healthy volunteers (22%) than subjects with IPF (8%, p<0.01). Yet, in the apical/basal or central/peripheral directions, barrier gradients were subtle (<10%) and were not significantly different between healthy subjects and subjects with IPF (p=0.63 and p=0.35, respectively). RBC transfer was characterised by a strong anterior to posterior gradient in healthy controls (mean=32%) that was eliminated in IPF (mean=2%, p<0.01). However, in IPF, RBC transfer exhibited a strong apical to basal gradient (−36%), significantly greater than in healthy volunteers (−12%, p=0.02). RBC transfer also exhibited a stronger central-peripheral gradient in IPF (−22%) than in healthy volunteers (−10%, p<0.01).

DISCUSSION

PFT correlations support functional imaging findings

The primary tools for diagnosing and monitoring IPF disease progression continue to be a combination of PFTs, CT scans and 6 min walk testing. Thus, the observation that ventilation MRI correlated only weakly with DL\(_{CO}\) and insignificantly with FVC suggests that its regional assessment does not provide a meaningful measure of disease severity in IPF. However, it is noteworthy that \(^{129}\)Xe MRI-derived barrier uptake, RBC transfer and RBC/barrier ratio correlated well with DL\(_{CO}\), a direct marker of global gas exchange. In particular, RBC/barrier was exceptionally well-correlated (r=0.94), thereby conferring it with a strong physiological grounding. Unlike DL\(_{CO}\), however, RBC/barrier can be further dissected to identify changes in barrier and RBC transfer individually, as well as how these are distributed regionally. Moreover, because these metrics are calculated using signals localised within the airspaces, this inherently accounts for differences in the volume of inhaled xenon, making it potentially less effort dependent.\(^{32}\)

Functional \(^{129}\)Xe MRI complements structural CT findings

The poor correlation between \(^{129}\)Xe MRI functional metrics and CT structural scores was particularly surprising. It is possible that these scores (which also correlated weakly and non-significantly with PFTs) reflect a limitation of the reader-based methodology. Recently, such reader methods were found inferior to computer-based CT analysis in predicting mortality in IPF,\(^{33}\) and one larger-scale study reported such more sophisticated densitometric and feature-based analysis to correlate positively with PFTs.\(^{34}\) However, a more fundamental explanation is that \(^{129}\)Xe MRI signal in barrier and RBC inherently arises only from the

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**Figure 3** Mean \(^{129}\)Xe ventilation correlates only modestly with FVC and DL\(_{CO}\). However, barrier uptake, RBC transfer and RBC/barrier ratio all correlate well with FVC and DL\(_{CO}\). The correlation between RBC/barrier and DL\(_{CO}\) (r=0.94) is particularly strong. In subjects with more than one MRI scan, correlation coefficients were calculated using all scans, while p values were derived using only the most recent time point to avoid assuming the independence of multiple measurements. DL\(_{CO}\), diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; RBC, red blood cell.
alveolar capillary unit and thus directly probes its function.\textsuperscript{35} Thus, one possible interpretation is that these direct regional gas exchange measurements are sensitive to disease at the alveolar level, which can differ from what might be inferred from large-scale structural findings on high-resolution CT.

The primary exception to the poor correlation between \textsuperscript{129}Xe MRI and CT was in late-stage IPF, where they appeared to agree visually, particularly in regions exhibiting extensive honeycombing. In such regions, both barrier uptake and RBC transfer were often diminished or absent. However, in less severe IPF, agreement was considerably weaker. In our cohort, we found numerous patients with definite UIP patterns on CT that did not demonstrate significantly impaired RBC transfer. In such cases, MRI paints a picture of preserved lung function despite extensive structural injury. On the other end of the spectrum, we also observed subjects where structural abnormalities were relatively few, but where MRI exhibited massive barrier enhancement throughout the lung, paired with regionally impaired RBC transfer. This may indicate significant disease activity that has not yet irreversibly remodelled the lung architecture.

**Functional imaging gradients consistent with normal physiology and fibrosis distribution**

It is encouraging that \textsuperscript{129}Xe MRI reveals spatial gradients that are consistent with both normal pulmonary physiology and the typical spatial patterns of disease in IPF. In a healthy subject lying supine, perfusion follows a gravitational gradient favouring the posterior lung.\textsuperscript{36} This was reflected in healthy volunteers exhibiting generally robust RBC transfer in the dependent lung, while any regions of low transfer were generally confined to the non-dependent, anterior slices. Similarly, barrier uptake also favoured the dependent lung in healthy subjects.

By contrast, such physiological gradients in \textsuperscript{129}Xe gas transfer were absent in IPF. Instead, barrier uptake was enhanced throughout the lung, consistent with a widespread pattern of fibrosis\textsuperscript{4} serving to override gravitational effects. Similarly, RBC transfer did not exhibit a gravitationally dependent pattern in IPF, possibly reflecting recruitment of gas exchange to anterior lung regions to maintain stable lung function.\textsuperscript{37} However, in the IPF cohort, several \textsuperscript{129}Xe spatial gradients emerged that were different from the healthy population. In particular, RBC transfer was significantly diminished in the basal and peripheral lung. This is where fibrosis and honeycombing are most commonly found on histology and CT.\textsuperscript{1,27}

**Models of gas transfer in IPF**

\textsuperscript{129}Xe MRI revealed four distinct patterns of gas exchange that often coexisted in the same patient (figure 5). The first is the essentially normal unit that predominates in healthy individuals (figure 5A), where inhaled \textsuperscript{129}Xe freely diffuses from the alveoli through the thin alveolar-capillary barrier to reach circulating RBCs. This results in barrier and RBC transfer being in the

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**Figure 4** Ventilation, barrier uptake and RBC transfer gradients in three directions. In both healthy subjects and subjects with IPF, ventilation gradients follow similar spatial patterns. Barrier transfer exhibits a spatial gradient only in the anterior-posterior direction of gravity and only in healthy lungs. A similar but stronger gradient in RBC transfer was present in healthy subjects but absent in IPF. In IPF, RBC transfer follows a large apical/basal gradient and a moderate central/peripheral gradient, consistent with known patterns of disease. IPF, idiopathic pulmonary fibrosis; RBC, red blood cell. μ - average difference, H - healthy, *statistically significant.
normal (green) range. Next is a region consistent with the classical model of diffusion limitation (figure 5B), where thickening of the alveolar–capillary membrane increases barrier uptake and delays transfer to capillary RBCs. Note that while xenon is classically considered to be a perfusion-limited gas, HP $^{129}$Xe MRI is inherently sensitive to diffusion impairment.

Figure 5C depicts a pattern that is seen in subjects with end-stage disease, characterised by regions with seemingly normal or even low barrier uptake but almost no RBC transfer. When examined on CT, these regions reveal severe fibrosis and honeycombing. We suggest that such regions represent severe and permanent scarring that impairs $^{129}$Xe uptake into the barrier tissue, thereby almost entirely eliminating its subsequent transfer to RBCs. Over time, such distortion would likely also lead to absent perfusion.

Moreover, perhaps most interesting, is figure 5D, which illustrates a pattern of greatly enhanced barrier uptake coexisting with preserved RBC transfer. This is unexpected from conventional models in which a thicker barrier should impair gas transfer to RBCs. However, this finding agrees with histological patterns of IPF, where patchy fibrotic zones, honeycomb changes and fibroblastic foci are known to coexist with regions of normal lung. Given the relatively modest resolution of the images (250 μm3), a single voxel contains over 40,000 alveoli, many of which could plausibly be normal. Combined with the known histopathological temporal heterogeneity in IPF, this pattern may represent early disease where fibrotic changes are below the resolution of conventional CT. Such at-risk regions may be particularly valuable to monitor as IPF progresses and could help identify areas where novel therapies may elicit a positive response.

**Study limitations and future directions**

Although $^{129}$Xe MRI shows promise in delivering a wealth of regional functional information, it will be critical to apply these methods to larger cohorts and to establish short-term reproducibility. In the present study, we can only estimate an initial upper bound on variability by examining one healthy subject and seven subjects with IPF in the study who were scanned at two time points (average 7.7 months apart). This yielded within-subject coefficients of variation of ±16% for barrier uptake, ±18% for RBC transfer and ±11% for RBC/barrier. However, given that this sample includes several patients with IPF who exhibited significant clinical disease progression between scans, this crude estimate clearly represents only an upper bound. Perhaps a more representative benchmark is the whole-lung RBC/barrier spectroscopic ratio, which was previously shown to exhibit a same day variability of ±6.6%.17

One limitation of our study was the use of younger subjects in our control group. Although this provides a useful starting reference, the ageing lung is known to undergo physiological changes in chest wall compliance, respiratory muscle function and the lung parenchyma, all with the potential to affect gas exchange.41 42 This, future studies may benefit from including an older, age-matched population of healthy controls. Furthermore, all subjects inhaled 1 L of gas regardless of their lung volumes, which may affect our functional metrics. However, in our preliminary studies of healthy individuals scanned at both Functional Residual Capacity (FRC) +1 L and after deliberate exhalation to FRC, gas transfer patterns were largely unchanged. Future studies would also benefit from determining and correcting for patient-specific haemoglobin levels.

We note several possible limitations that could explain the much stronger correlation of $^{129}$Xe MRI to PFTs. First, CT scoring was only available in the IPF cohort. However, even when eliminating healthy subjects from analysis, the $^{129}$Xe–PFT correlations remained robust for RBC/barrier with FVC (r=0.57, p=0.01) and DLCO (r=0.80, p=0.01). We also note that several subjects in the IPF cohort had CT and MRI scans several months apart. However, other studies of quantitative CT biomarkers in IPF detected changes in CT score over a 7-month period of...
REFERENCES