



Xenon-129 magnetic resonance imaging and spectroscopy detects response to therapy in pulmonary hypertension

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Xenon-129 gas-exchange magnetic resonance imaging/magnetic resonance spectroscopy (^{129}Xe MRI/MRS) is an emerging functional lung imaging technology with the potential to provide precise, spatial, quantitative metrics of pulmonary ventilation, interstitial membrane uptake, transfer to capillary red blood cells (RBCs) and haemodynamics [1–3]. When used in concert, these ^{129}Xe MRI/MRS metrics can be used to differentiate between patients with COPD, idiopathic pulmonary fibrosis (IPF), pulmonary arterial hypertension (PAH) and post-capillary pulmonary hypertension (PH) [3]. Incorporation of cardiogenic ^{129}Xe -RBC signal oscillations and RBC transfer defects into an initial diagnostic algorithm revealed good sensitivity and specificity in differentiating between pre- and post-capillary PH [4]. However, it is not known whether these ^{129}Xe -RBC metrics are sensitive to changes associated with PAH-targeted therapies. Here, we addressed this question by performing a descriptive proof-of-concept study using these markers to measure therapy response in PH patients treated with inhaled treprostinil (iTRE).

This institutional review board-approved prospective study recruited 11 subjects with a diagnosis of PH on treatment with iTRE. At the time of the study, haemodynamic inclusion criteria for group 1 PH were mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg in the absence of significant concomitant left heart disease or lung disease, for group 2 PH were mPAP ≥ 25 mmHg and PCWP > 15 mmHg in the absence of significant concomitant lung disease, and for group 3 PH were mPAP ≥ 25 mmHg and PCWP ≤ 15 mmHg in the setting of chronic lung disease. Patients with group 2 and 3 PH included in this study had been started on iTRE by their outpatient physicians and all had pulmonary vascular resistance ≥ 4 Wood units. ^{129}Xe gas exchange dynamic spectroscopy and imaging (figure 1a) were acquired according to consortium recommendations [5] using dose equivalents [6] of 72 ± 11 mL and 167 ± 72 mL, respectively. Acquisitions were compared at anticipated trough level serum treprostinil concentration (last treatment the evening prior), at predicted peak serum level (15 min after iTRE treatment), and at predicted trough serum level (3 h after treatment) (figure 1b). Spectroscopy was used to calculate RBC:membrane ratio and RBC oscillation amplitude. Imaging was used to generate maps of RBC transfer that were quantified using thresholds based on a multi-site healthy reference population of 32 healthy 18- to 30-year-old subjects (50% females) [7]. The percentage of the lung exhibiting low signal was defined as areas within the lung mask, with signal falling more than one standard deviation below the reference mean [7]. Regions containing ventilation defects were excluded from analysis of RBC signal. All subjects ($n=11$) were included in the analysis of RBC:membrane and low RBC transfer percentage. Unfortunately, intermittent scanner noise caused most RBC oscillation data to have insufficient signal-to-noise ratio for analysis [8], and were thus excluded. Changes at 15 min and 3 h were compared to baseline using Friedman's test with multiple comparisons testing using GraphPad Prism. A p-value of < 0.05 was considered statistically significant.

Six subjects had group 1 PH, three had group 3 PH, and two had group 2 PH. Baseline ^{129}Xe MRI/MRS patterns were consistent with the clinical presence of comorbidities such as COPD and interstitial lung disease (ILD). Consistent with previous studies [3, 4], subjects with groups 1 and 2 PH displayed relatively normal airspace and membrane signal with a decrease in RBC signal, while group 3 PH patients with COPD predominantly displayed airspace defects, and those with ILD showed increased membrane signal (figure 1c). iTRE treatment caused no statistically significant changes in abnormal airspace signal.

Shareable abstract (@ERSpublications)

This work provides proof-of-concept for ^{129}Xe gas-exchange magnetic resonance imaging/MR spectroscopy as a surrogate marker to measure therapy response in pulmonary hypertension
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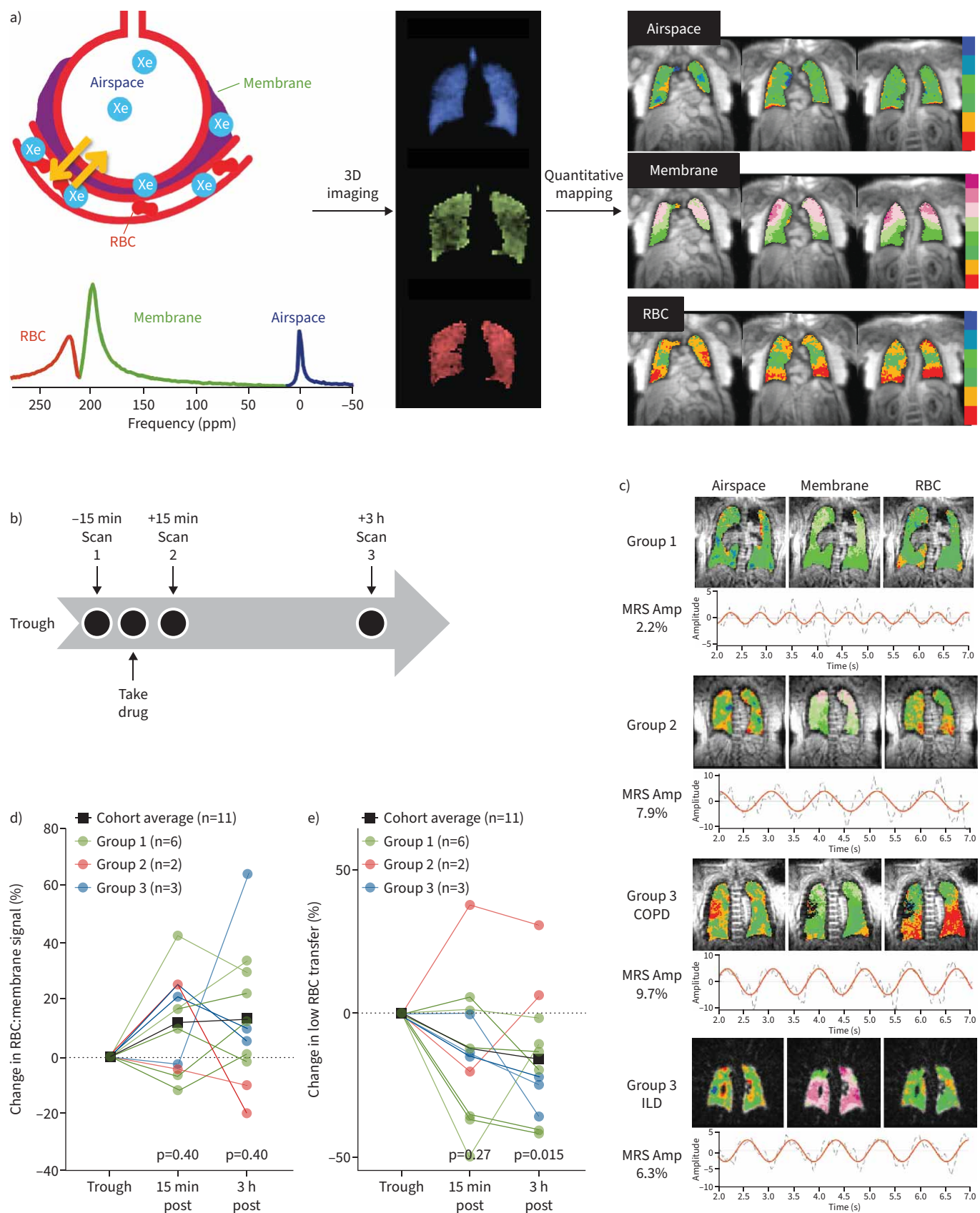


FIGURE 1 Inhaled treprostinil promotes increased pulmonary capillary blood volume in pulmonary hypertension (PH). **a)** Hyperpolarised xenon-129 freely diffuses from the airspaces, into membrane (lung parenchyma), and red blood cells (RBCs), where it exhibits distinct frequency

shift (left). The signal in each compartment can be imaged in three dimensions (centre) in a single breath, and quantitatively mapped (right). **b)** Design of this study to assess changes in ^{129}Xe magnetic resonance imaging signal with inhaled treprostinil treatment, in which subjects stably treated with drug presented at the start of the day prior to drug treatment (trough) for their first scan. The acute effect of inhaled treprostinil was assessed at 15 min, while any longer-term effect was measured at 3 h. **c)** Representative baseline images and cardiogenic RBC oscillations for group 1, 2 and 3 PH (COPD and interstitial lung disease, ILD). Relative to their baseline values, **d)** RBC:membrane signal did not demonstrate a statistically significant improvement at 15 min or 3 h, while **e)** changes in low RBC transfer percentage were statistically significant 3 h after inhaled treprostinil treatment (Friedman's test with multiple comparisons testing). MRS: magnetic resonance spectroscopy.

The mean membrane:gas did not change significantly at 15 min ($p=0.52$) or 3 h ($p=0.07$). Mean RBC:gas also did not change significantly from baseline at 15 min ($p=0.85$) and 3 h ($p=0.09$); however, mean RBC:gas did increase by 21% at 3 h.

After iTRE therapy, the patterns of global RBC:membrane ratio and low RBC transfer percentage were largely consistent, with a similar pattern between subjects (as both are quantification of changes in RBC signal) (figure 1d and e). The changes in RBC:membrane were not statistically significant ($p=0.40$), while the change in low RBC transfer percentage was not significant at 15 min ($p=0.27$), but reached significance at 3 h ($p=0.015$). While the 3-h time-point was designed to be a "trough" time-point based on the predicted serum concentration of treprostinil, our findings suggest that the effects of treprostinil in the lungs persist even when serum concentrations of the drug are low. There also appeared to be a pattern of subject-specific responses to iTRE that may be related to their comorbidities, with the two group 2 PH patients displaying a lack of improvement in low RBC transfer percentage compared to the group 1 and 3 PH patients; however, the low number of patients in each precluded statistical comparison (figure 1d and e).

This is the first study to investigate the ability of ^{129}Xe MRI/MRS as a noninvasive imaging biomarker to study response to therapy in PH. This study found low RBC transfer percentage was sensitive to physiological changes associated with iTRE, consistent with increased pulmonary capillary blood volume upon treatment [9]. The effect was likely caused by vasodilation, but was subtle as this study was conducted in patients already on background therapy. However, these observations suggest that this technology could sensitively monitor changes associated with chronic PAH-targeted therapies. Such technologies to predict long-term responses to PAH-targeted therapies are a major unmet need in PH, especially in the setting of concomitant heart and lung disease. The benefit of iTRE was demonstrated in the INCREASE study, as it is now the first medication specifically approved for PH-ILD [10–12]. This pivotal trial showed iTRE therapy significantly improved PH-ILD functional capacity (as assessed by 6-min walk distance, 6MWD), disease severity (reflected by circulating natriuretic peptide levels, NT-proBNP), and clinical course (fewer ILD exacerbations and a slower rate of vital capacity decline). In INCREASE, patients with IPF improved their 6MWD while those with combined pulmonary fibrosis and emphysema did not. Currently, there are no validated prognostic metrics for identifying which PH-ILD patients are most likely to benefit from inhaled prostacyclin therapy [13–15]. Subject to future, larger studies, our work suggests hyperpolarised ^{129}Xe MRI and MRS could provide such information. This technology provides individualised assessment of lung function and, potentially, personalisation of therapy. These biomarkers may also aid in decisions regarding when and which treatment should be introduced, or when to escalate or de-escalate treatment.

While a small study, this work provides proof-of-concept for ^{129}Xe MRI/MRS as a surrogate marker in PAH. Such biomarkers could potentially provide more precise measurements, allowing greater reliability of pathophysiological effects of treatment and more rapid progress of clinical trials toward clinical implementation of new treatments. Such precise measurements, when validated with clinically relevant endpoints, would provide increased power and allow smaller populations in early phase clinical trials. Second, it demonstrates the potential value of novel imaging approaches, and MRI in particular, which can provide additional information beyond current clinically used noninvasive assessments (6MWD and NT-proBNP) that are largely disease non-specific. In the future, these types of technologies may allow greater individualised assessment of lung function and the impact of new treatments, thus personalising therapy. Our study also had several limitations, including a small sample size and being limited to assessing only acute response of one US Food and Drug Administration-approved PAH-targeted therapy (iTRE) in a heterogeneous patient cohort. However, iTRE was chosen because its pharmacokinetics would allow an assessment of an acute response, and the cohort reflected real-world clinical practice.

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