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Longitudinal follow-up of postacute COVID-19 syndrome: DL_{CO}, quality-of-life and MRI pulmonary gas-exchange abnormalities

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ABSTRACT

^{129}Xe MRI red blood cell to alveolar tissue plasma ratio (RBC:TP) abnormalities have been observed in ever-hospitalised and never-hospitalised people with postacute COVID-19 syndrome (PACS). But, it is not known if such abnormalities resolve when symptoms and quality-of-life scores improve. We evaluated 21 participants with PACS, 7±4 months (baseline) and 14±4 months (follow-up) postinfection. Significantly improved diffusing capacity of the lung for carbon monoxide (DL_{CO}, Δ=14%$_{pred}$;95%CI 7 to 21, p<0.001), postexertional dyspnoea (Δ=−0.7; 95%CI=−0.2 to −1.2, p=0.019), St George's Respiratory Questionnaire-score (SGRQ Δ=−6; 95% CI=−1 to −11, p=0.044) but not RBC:TP (Δ=0.03; 95% CI=0.01 to 0.05, p=0.051) were observed at 14 months. DL_{CO} correlated with RBC:TP (r=0.60, 95% CI=0.22 to 0.82, p=0.004) at 7 months. While DL_{CO} and SGRQ measurements improved, these values did not normalise 14 months post-infection. ClinicalTrials.gov NCT04584671.

INTRODUCTION

In patients with postacute COVID-19 syndrome (PACS), fatigue, chest pain, brain fog and dyspnoea are common and contribute to poor quality of life (QoL).[1 2] Recent studies showed that 7%–30%[1 3] of people with PACS remain symptomatic 1–6 months postinfection. Unfortunately, the underlying mechanisms and pathologies responsible for PACS are not well understood.

Chest CT measurements of abnormal pulmonary vascular blood distribution[4] and fibrosis[5] have been reported in patients following recovery from COVID-19 infection. Hyperpolarised ^{129}Xe MRI has also revealed alveolar gas-transfer abnormalities in PACS,[6 7 7] including in never-hospitalised people up to 41 weeks postinfection.[8] However, longitudinal ^{129}Xe measurements have not been reported and previous studies did not have access to pre-COVID-19 imaging to inform on potential mechanisms linking symptoms and gas-exchange abnormalities.[7 8] Here, we endeavoured to determine whether ^{129}Xe MRI gas-transfer measurements normalised over time in people with PACS and if such changes occurred in concert with improved QoL and DL_{CO} measurements.

METHODS

We obtained written-informed consent from participants 18–80 years of age for this prospective study. Participants with a previous positive PCR COVID-19 test and ongoing symptoms were recruited from a local COVID-19 clinic. Study visits were planned for 3±1 months (baseline) and 15±3 months (follow-up) post-COVID-19+ test. Participants underwent ^{129}Xe ventilation MRI, ^{129}Xe gas-transfer MRI, spirometry, diffusing capacity of the lung (DL_{CO}) measurement, fraction of exhaled nitric oxide (FeNO) measurement, 6 min walk test (6MWT) and the St. George's Respiratory Questionnaire (SGRQ). The ^{129}Xe MRI red blood cell (RBC) to alveolar tissue plasma (TP) ratio was the primary endpoint. SPSS (SPSS Statistics V.27.0; IBM) was used for all statistical analyses. Data were tested for normality using Shapiro-Wilk tests and nonparametric tests were performed for non-normally distributed data. Correlations were evaluated using Pearson (r) and Spearman (ρ) correlations. Pearson and Spearman correlations at baseline and follow-up were compared using the Fisher's z-score. Repeated measures were tested using paired t-tests. Results were considered statistically significant when the probability of making a type I error was <5% (p<0.05). Detailed methods are provided in online supplemental file 1. Baseline results were previously reported.[8]

RESULTS

At baseline, we enrolled 34 participants[8] and 21 of these (7 female, age=56±15 years) returned for follow-up. For these 21 participants with PACS, the baseline visit occurred 7±4 months post-COVID-19 infection with positive tests occurring during the period March 2020 to April 2021, which was prior to the population-based vaccination initiatives in our local area. The follow-up visit occurred 14±4 months post-COVID-19 infection. Participant demographics are detailed in online supplemental e-Table 1. Nine of these participants were hospitalised due to COVID-19 infection, and one required intubation during a 4-week intensive care unit admission. Five participants were diagnosed with pulmonary embolism (via CT angiogram) during their COVID-19 infectious period. Medications are summarised in online supplemental e-Table 2.

Figure 1 summarises baseline and follow-up clinical, QoL and imaging measurements in tabular format and spaghetti plots for DL_{CO}, SGRQ and ^{129}Xe MRI measurements. There were no significant

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A

	Baseline (n=21)	Follow-up (n=21)	Difference [95% CI]	Significance (p)
Days Since +	198 (131)	420 (120)	222 [199,245]	
FEV_1 $\%_{pred}$	92 (22)	92 (22)	-0.4 [-2.8,2]	.729
FVC $\%_{pred}$	91 (21)	93 (27)	3 [-5.2,11.2]	.555
FEV_1/FVC %	78 (11)	78 (13)	-0.4 [-4.4,3.6]	.888
FeNO	24 (16)*	21 (15)*	-3 [-6,-1]	.084
$DL_{CO}\%_{pred}$	81 (20)*	96 (23)*	14 [7,21]	**<.001**
Quality-of-Life				
SGRQ	33 (20)	27 (21)	-6 [-11,-1]	**.044**
Symptom	42 (23)	31 (26)	-11 [-20,-2]	**.032**
6MWD m	409 (75)	431 (88)	22 [0,44]	.079
mBDS post-exertion	2.0 (1.5)	1.5 (1.8)	-0.7 [-1.0,-0.4]	**.019**
^{129}Xe MRI				
VDP	5 (9)*	4 (9)*	-0.3 [-1.2,0.6]	.500
RBC:TP	0.32 (0.09)	0.35 (0.09)	0.03 [0.01,0.05]	.051
TP:gas	1.11 (0.28)	1.13 (0.26)	0.02 [-0.06,0.05]	.659
RBC:gas	0.35 (0.14)	0.40 (0.16)	0.05 [0.01,0.09]	.055

B

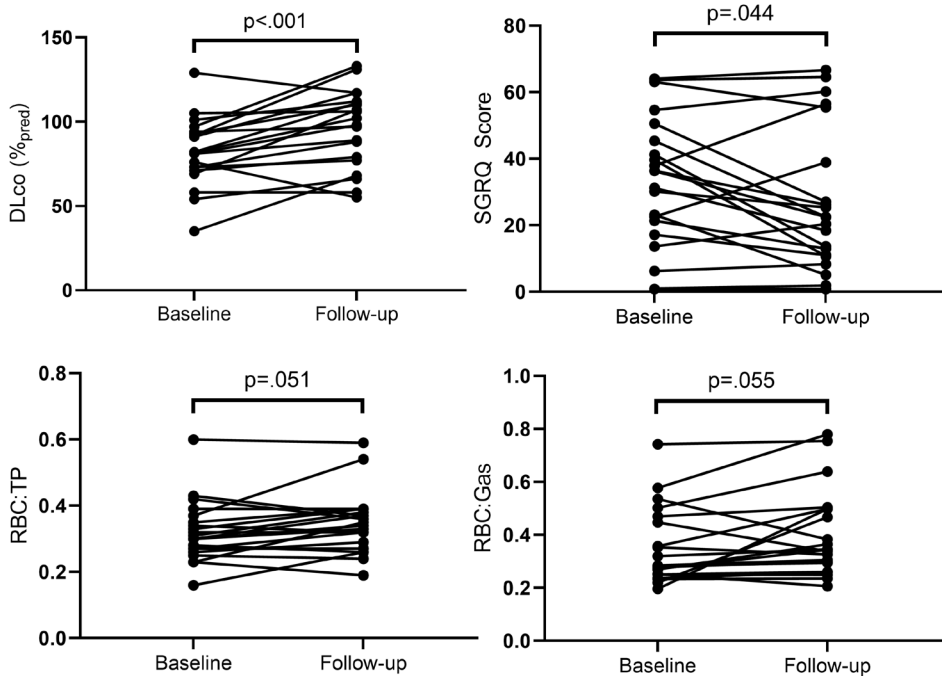

Figure 1 Clinical, quality of life and imaging measurements at baseline (7±4 months since PCR test) and follow-up (14±4 months since PCR test). (A) shows tabulated baseline and follow-up measurements. (B) provides spaghetti plots for DL_{CO}, SGRQ score, ^{129}Xe MRI RBC:TP and RBC:gas measurements at baseline and follow-up. Differences were analysed for significance using paired t-tests. *n=20. 6MWD, 6 min walk distance; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 s; $\%_{pred}$, per cent of predicted value; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; mBDS, modified Borg Dyspnoea Scale; RBC, red blood cell; SGRQ, St. George's Respiratory Questionnaire; TP, tissue plasma.

differences in spirometry, 6MWD (Δ=22;95% 95% CI=0 to 44, p=0.084) and FeNO (Δ=−3; 95% CI=−6 to −1, p=0.084) between visits; FeNO measurements were normal across visits. DL_{CO} (Δ=14; 95% CI=7 to −21, p<0.001), SGRQ-total (Δ=−6; 95% CI=−1 to −11, p=0.044) and symptom-score (Δ=−11; 95% CI=−2 to 20, p=0.032) significantly improved at follow-up. There was also significantly improved postexertional dyspnoea (measured using the modified Borg Dyspnoea Scale post-6MWT, Δ=−0.7; 95% CI=−0.2 to −1.2, p=0.019) but not ^{129}Xe RBC:TP (Δ=0.03; 95% CI=0.01 to 0.05, p=0.051), ^{129}Xe RBC:gas (Δ=0.06; 95% CI=0.02 to 0.10, p=0.055) or FeNO (Δ=−3; 95% CI=0 to −6, p=0.084) at 14 months. At baseline, two participants desaturated (ΔSpO_2=−9%, −7%) following the 6MWT while at follow-up, no participants desaturated.

Figure 2 shows representative three-dimensional ^{129}Xe MRI RBC maps coregistered with the corresponding segmented CT vessel tree for a single 31-year-old male participant at baseline and follow-up. ^{129}Xe MRI RBC map focal defects were obvious in the left and right lower lobes at baseline (shown in the insets) and this was coincident with an SGRQ total score of 23, postexertional breathlessness score of 3 and RBC:TP ratio of 0.37. At

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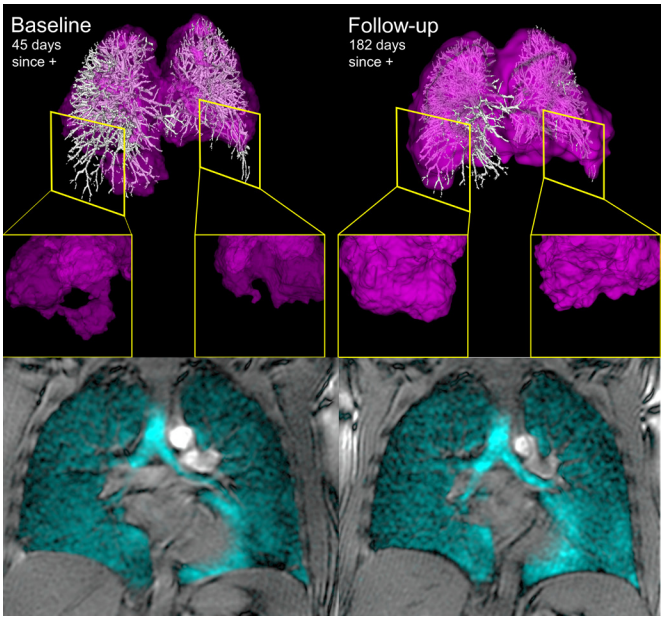

Figure 2 ^{129}Xe MRI and coregistered pulmonary vascular tree CT at baseline and follow-up. Left and right panels show ^{129}Xe MRI RBC map (pink) coregistered with CT pulmonary vascular tree (white) and bottom panels show ^{129}Xe ventilation images (cyan) for a previously healthy participant hospitalised with COVID-19 symptoms and pulmonary embolism. At baseline, 45 days post-COVID-19 positive test, RBC:TP ratio was abnormally low (0.37) and insets provide examples of RBC map defects. At follow-up the RBC:TP ratio improved (0.54) as did the lower lobe red blood cell map defects shown in the right panel inset. DL_{CO} (baseline=93%pred, follow-up=110%pred) and total SGRQ score. (baseline=23, follow-up=5) also improved at follow-up. DL_{CO}, diffusing capacity of the lung for carbon monoxide; RBC, red blood cell; SGRQ, St George's Respiratory Questionnaire.

follow-up, shown in the right panel, the RBC defects visually improved and this was coincident with clinically relevant improvements[9] in SGRQ total score of 5, postexertional breathlessness score of 1 and improved RBC:TP ratio (0.54). Online supplemental e-Figure 1 shows multiple slices of ventilation and two dimensional raw RBC component of the dissolved phase images at both baseline and follow-up for additional participants.

Figure 3A shows weak-to-moderate correlations for DL_{CO} and ^{129}Xe MRI RBC:TP (r=0.60 95% CI=0.22 to 0.82, p=0.004) and RBC:Gas (ρ=0.48, 95% CI=0.04 to 0.76, p=0.029) at baseline. Figure 3B shows DL_{CO} correlations at follow-up (RBC:TP r=0.47, 95% CI=0.04 to 0.76, p=0.035; RBC:Gas, ρ=0.57, 95% CI=0.16 to 0.81, p=0.009). The correlations for DL_{CO} and RBC:TP at baseline (r=0.60, p=0.004) and follow-up (r=0.47, p=0.03) were not significantly different (z score=0.51, p=0.609). Online supplemental e-Figure 2 shows significant correlations for the change in SGRQ at follow-up with the change in DL_{CO} (r=−0.55, CI=−0.14 to −0.80, p=0.012) and postexertional Borg dyspnoea (r=0.68, 95% CI=0.35 to 0.86, p=0.001).

DISCUSSION

Previous work revealed the presence of ^{129}Xe gas-transfer abnormalities in people with PACS,[7 8] and showed that these abnormalities were related to dyspnoea and exercise limitation.[8] We examined a small group of 21 participants with PACS to measure SGRQ, DL_{CO} and ^{129}Xe MRI gas-exchange measurements, 7 months after a baseline visit and observed: (1) significant improvements in DL_{CO}, SGRQ scores and postexertional dyspnoea, (2) persistently abnormal ^{129}Xe MRI RBC:TP values, (healthy volunteer RBC:TP=0.41±0.10)[8] and (3) positive correlation for DL_{CO} with ^{129}Xe MRI RBC measurements, negative correlation for the change in DL_{CO} with the change in SGRQ and a positive correlation for the change in DL_{CO} with postexertional dyspnoea at follow-up. Whether this snapshot in time, 14±2 months postinfection reflects a slow, ongoing recovery or permanent impairment, remains to be ascertained.

Previous work[8] detected a significant correlation between DL_{CO} and ^{129}Xe RBC:TP in PACS and here, we observed that this correlation persisted over time. This suggested that ^{129}Xe RBC:TP detected abnormal alveolar gas-exchange that remained abnormal in people with PACS, long after the infection had resolved. We also observed a correlation between postexertional dyspnoea and DL_{CO} on SGRQ-score, underscoring the impact

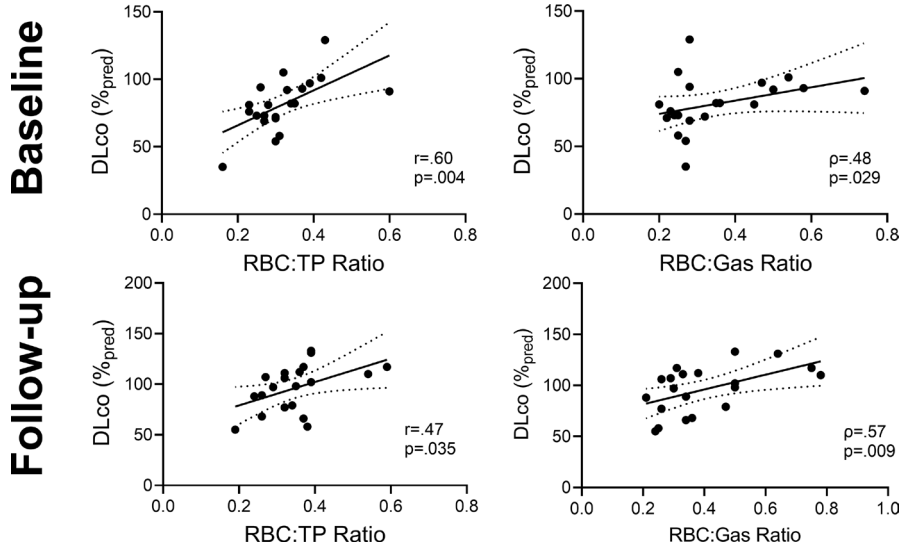

Figure 3 Correlations between DL_{CO} and ^{129}Xe MRI measurements. At baseline and follow-up, there were weak to moderate, significantcorrelations between DL_{CO} and ^{129}Xe MRI RBC:TP and RBC:gas ratios. (Participants with DL_{CO} measurement n=20). DL_{CO}, diffusing capacity of the lung for carbon monoxide; RBC, red blood cell; TP, tissue plasma.

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of dyspnoea and gas-exchange improvements on QoL improvements in PACS.

Together, these data suggest gas-exchange abnormalities at least partially resolved during a period of 7 months (and 14 months postinfection). While we do not know the precise cause of abnormal RBC:TP in these participants, a recently published study that evaluated postmortem COVID-19 lungs described vasculo pathologies including vascular congestion, perivascular inflammation, thromboemboli and infarcts unique to COVID-19 that could explain ongoing pulmonary vascular abnormalities.[10]

To our knowledge, this is the first longitudinal ^{129}Xe gas-transfer MRI study of PACS. This study was limited by small sample size. ^{129}Xe spectroscopy had not previously been performed at our site and this study was, therefore, not powered for spectroscopy measurements. The sample size was also limited by incomplete retention of the original cohort of study participants. Retention difficulties stemmed from a number of reasons including the fact that fully recovered participants were less inclined to return for a follow-up visit during the COVID-19 pandemic and because of institutional requirements for fully vaccinated participants at follow-up. We also note that measurements were not available in these participants prior to infection and this makes it difficult to distinguish abnormalities due to PACS or other sources. In particular, seven patients had pre-existing asthma and one had pre-existing COPD, which may have impacted gas-exchange measurements.

We measured improved SGRQ, DL_{CO} and postexertional dyspnoea 14 months as compared with 7 months postinfection. Taken together, these findings provide hypothesis-generating insights, which may help target future research on the mechanisms of gas-exchange abnormalities in people with PACS.

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Contributors AMM, MJM and HKK were responsible for data acquisition and analysis. AMM was responsible for preparing the first draft of the manuscript. ID and JN were responsible for recruiting study participants and providing clinical input and interpretation of the data. MA, MSA, AO and SS supported the study design development and interpretation of the data. GP was responsible for study design, data analysis and interpretation as well as being the guarantor of study data integrity. All authors had an opportunity to review and revise the manuscript and approved its final submitted version.

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Competing interests SS has received honoraria for speaking engagements from AstraZeneca, Novartis and Polarean, personal fees from Arrowhead Pharma and received study funding from Cyclomedia, none of which was related to this work. JN has received honoraria from AstraZeneca, Horizon Therapeutics and Vertex outside the submitted work. GP has received research support and consulting fees from Novartis and AstraZeneca and personal fees for speaking engagements from AstraZeneca and Polarean Imaging. AMM, MJM, HKK, MA, MSA, ID and AO have no conflicts to declare.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Western University Health Science Research Ethics Board #113224. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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Longitudinal follow-up of post-acute COVID-19 syndrome: DL_{CO}, QoL and MRI pulmonary gas-exchange abnormalities.

ONLINE DATA SUPPLEMENT

Material and Methods

Study Participants

We prospectively evaluated people 18-80 years of age who provided written-informed-consent to an ethics-board (HSREB # 113224), Health-Canada approved and registered protocol (ClinicalTrials.gov: NCT04584671). Study participants with a proven positive PCR COVID-19 test were prospectively recruited from a quaternary-care COVID-19 clinic between April and October 2021. Inclusion criteria consisted of: age ≥ 18 and <80 years, a documented case by positive RT-PCR test of COVID-19 infection that resulted in symptoms post-infection. Exclusion criteria consisted of: contraindications to MRI such as implants and severe claustrophobia, mental or legal incapacitation or could not read or understand written material, inability to perform spirometry or plethysmography maneuvers, and pregnancy.

Study Design

The study design consisted of Visit 1 (3-months post +COVID test), an optional Visit 2 (9-months post +COVID test), Visit 3 (15-months post +COVID test) and Visit 4 (27-months post +COVID test). Participants were administered salbutamol upon arrival at our centre according to American Thoracic Society Guidelines(1) and 15 minutes later performed post-bronchodilator (BD) spirometry and DL_{CO} immediately prior to MRI. Participants completed the six-minute-walk-test (6MWT) and Questionnaires (St. George's Respiratory Questionnaire (SGRQ),(2) modified Medical Research Council (mMRC) Questionnaire, Chronic Obstructive Pulmonary Disease

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Assessment Test (CAT),(3) post-COVID-19 Functional Status scale,(4) International Physical Activity Questionnaire (IPAQ),(5) and modified Borg Dyspnoea Scale (mBDS).(6, 7) ^{129}Xe gas-exchange MRI was performed in at least two visits. SpO_2 and heart rate were measured using an 8500 series handheld pulse oximeter (Nonin Medical Inc.) upon participant arrival as well as before and just after the 6MWT.

Pulmonary Function Tests

Pulmonary function tests were performed according to American Thoracic Society guidelines(8, 9) using a *ndd EasyOne Pro LAB system* (ndd Medical Technologies) or a *MedGraphics Elite Series* plethysmograph (MGC Diagnostics Corporation). Post-BD measurements were performed 15 minutes after inhalation of 4×100 µg/inhalation salbutamol sulfate norflurane (Ivax Pharmaceuticals) using an *AeroChamber* (Trudell Medical International). Participants underwent FeNO measurement according to guidelines(10) using a NIOX VERO system (Circassia Pharmaceuticals, Inc.). Participants withheld inhaled medications before study visits according to American Thoracic Society guidelines (e.g. short-acting β-agonists ≥6 hours, long-acting β-agonists ≥12 hours, long-acting muscarinic antagonists ≥24 hours).(8) Questionnaires and the 6MWT were self-administered under supervision of study personnel.

^{129}Xe MRI

Anatomic ^{1}H MRI was acquired using a fast-spoiled gradient-recalled-echo sequence (partial-echo acquisition; total acquisition time, 8 seconds; repetition-time msec/echo time msec, 4.7/1.2; flip-angle, 30°; field-of-view, 40×40cm^2; bandwidth, 24.4 kHz; 128×80 matrix, zero-filled to 128×128; partial-echo percent, 62.5%; 15-17×15mm slices). ^{129}Xe MR spectroscopy was acquired following inhalation breath-hold of a 1.0L gas mixture (4/1 by volume 4He/129Xe) from functional residual capacity (FRC) using a free-induction-decay whole-lung spectroscopy sequence (200 dissolved-

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phase spectra, TR=15ms, TE=0.7ms, flip=40°, BW=31.25kHz, 600μs 3-lobe Shinnar-Le Roux pulse). Spectroscopy was used to determine the echo time for a 90° tissue-plasma/RBC phase difference (TE_{90}). ^{129}Xe MRI was performed following inhalation of a 1.0L gas mixture (1/1 by volume ^{4}He/^{129}Xe) using an interleaved gas/dissolved-phase 3D radial sequence (TR=15ms TE=variable, flip=0.5°/40°, FOV=40cm^3, matrix=72x72x72, BW=62.5kHz, 990 gas/dissolved projections, 600μs 3-lobe Shinnar-Le Roux pulse, frequency shift=7.664kHz). Supine participants were coached to inhale a 1.0L bag (Tedlar; Jensen Inert Products, Coral Springs, FL, USA) (500mL ^{129}Xe + 500mL ^{4}He for ^{129}Xe MRI and 1.0L N_2 for ^{1}H MRI) from the bottom of a tidal breath (functional residual capacity) with acquisition under breath-hold conditions. ^{129}Xe gas was polarised to 30-40% (Polarean; Xenispin 9820, Durham, NC, USA).(11)

Gas-transfer MRI data were reconstructed as previously described using a re-gridding method for non-cartesian acquisition.(12) Receiver phase-offset and local phase inhomogeneity were corrected as previously described.(13)

^{129}Xe gas-exchange MRI were corrected for local phase inhomogeneity using acquired interleaved gas-compartment data. Deviations from uniform phase in the gas image were assumed to result from phase inhomogeneity and voxel-wise phase corrections were applied to eliminate inhomogeneity effects. Receiver phase-offset was corrected using the spectroscopic RBC:TP ratio. A phase correction $\Delta\phi$ was applied such that the ratio of real to imaginary channel signal matched the spectroscopic RBC:TP ratio under the assumption that RBC and TP signal should be perfectly aligned to the real and imaginary channels, respectively, at TE_{90}.

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TABLES

e-Table 1. Participant Demographics

Parameter Mean (SD)	PACS (n=21)
Age yrs	56 (15)
Females n (%)	8 (38)
Hospitalized n (%)	9 (43)
BMI kg/m^2	31 (6)
Asthma n (%)	7 (33)
COPD n (%)	1 (5)
Pack-years	8 (19)

BMI=body mass index; COPD=chronic obstructive pulmonary disease

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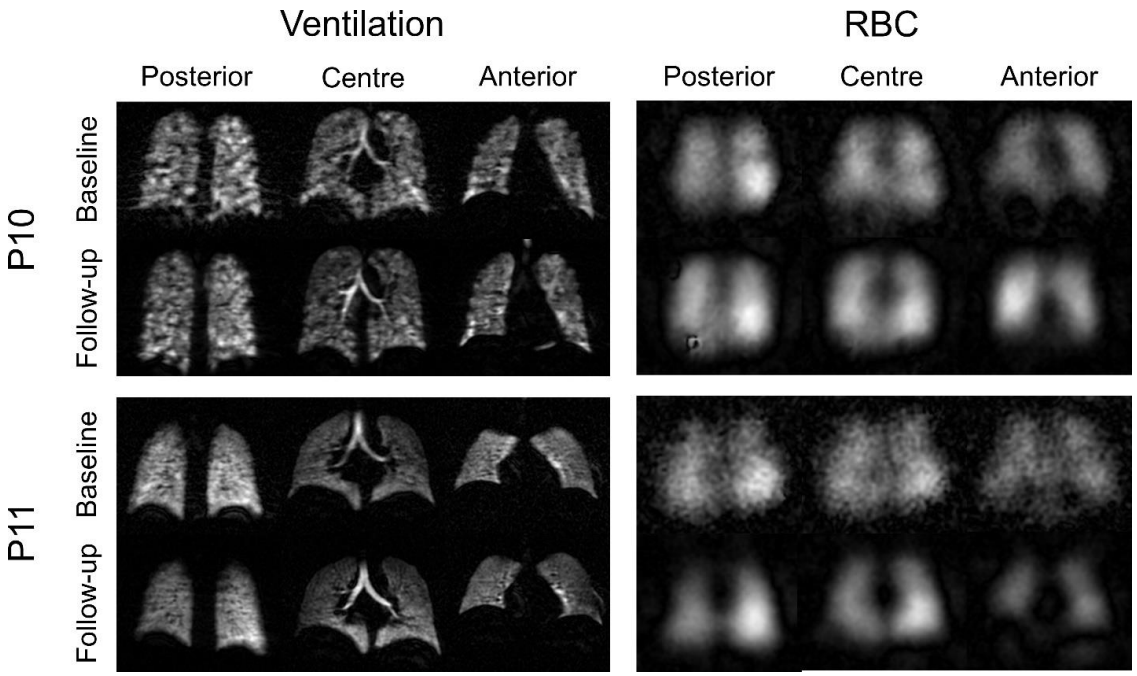
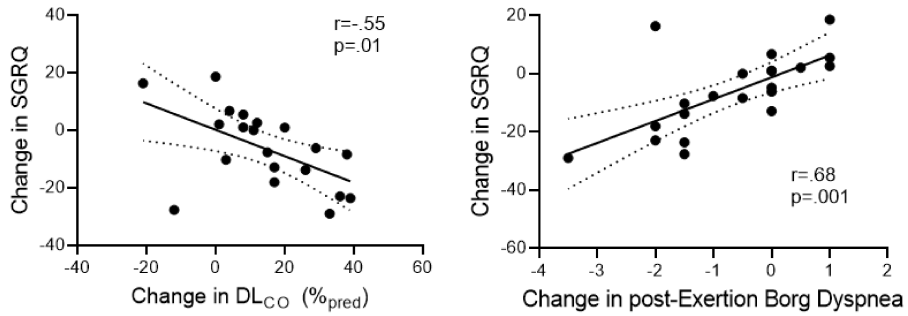
e-Table 2. Participant medications

Participant	Baseline Medications	Follow-up Medications
P01	Anticoagulant, ICS/LABA, SABA	Anticoagulant, ICS/LABA, SABA
P02	ICS/LABA, Anticholinergic, ICS	ICS/LABA, SABA
P03	ICS/LABA, ACE inhibitor, BP	ICS/LABA, ACE inhibitor, BP
P04	ICS/LABA	None
P05	Anticoagulant, stimulant	Anticoagulant, stimulant
P06	Diuretic, anticoagulant, thyroid hormone, BP	ICS/LABA, Diuretic, anticoagulant, thyroid hormone, BP
P07	Alpha blocker, beta blocker, anticoagulant, anti-cholesterol, BP, ICS	Alpha blocker, beta blocker, anticoagulant, anti-cholesterol, BP, ICS
P08	Antidepressant, ICS/LABA	ICS/LABA
P09	Antidepressant	Antidepressant
P10	ICS/LABA, Leukotriene antagonist, LABA, proton pump inhibitor	ICS/LABA, SABA, leukotriene antagonist, LABA, proton pump inhibitor, ICS
P11	ISC/LABA, SABA	ICS/LABA
P12	None	None
P13	BP, anti-cholesterol, alpha blocker, beta blocker, proton pump inhibitor, aspirin, ICS/LABA	BP, anti-cholesterol, alpha blocker, beta blocker, proton pump inhibitor, aspirin, diuretic, ICS/LABA
P14	Thyroid hormone, antidepressant	Thyroid hormone, contraceptive
P15	Insulin, acetaminophen, anti-cholesterol, anticoagulant, anti-inflammatory, proton pump inhibitor, ICS/LABA, SABA, beta agonist	Insulin, acetaminophen, anti-cholesterol, anticoagulant, ani-inflammatory, opioid, BP
P16	Acetaminophen, anticonvulsant, anti-inflammatory, hormone	Anticonvulsant, antidepressant, anti-inflammatory
P17	ACE inhibitor, BP, proton pump inhibitor, prostaglandin analog, anti-cholesterol, LABA, SABA, aspirin, ICS/LABA	ACE inhibitor, BP, proton pump inhibitor, prostaglandin analog, anti-cholesterol, LABA, SABA, aspirin, ICS/LABA
P18	Monoclonal antibody, digestive enzyme, ICS/LABA, SABA, LABA, anti-histamine	Monoclonal antibody, digestive enzyme, ICS/LABA, SABA, LAMA
P19	Antidepressant	ICS/LABA, BP
P20	Anti-cholesterol, prostaglandin analog, diuretic, antacid, SABA	Anti-cholesterol, prostaglandin analog, diuretic, antacid, SABA
P21	None	None



eFigure 1. Ventilation imaging and 2D (three central slices) raw red blood cell component of the dissolved phase images at baseline and follow-up for two participants.

Matheson AM, *et al. Thorax* 2023;0:1–4. doi: 10.1136/thorax-2022-219378



e-Figure 2. Correlations between changes in SGRQ score and clinical measurements. There were moderate correlations between changes in SGRQ score and changes in DL_{CO} as well as post-exertion Borg dyspnoea. (Participants with DL_{CO} measurement n=20).

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