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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

¹²⁹Xe 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 distribution⁴ and fibrosis⁵ have been reported in patients following recovery from COVID-19 infection. Hyperpolarised ¹²⁹Xe MRI has also revealed alveolar gas-transfer abnormalities in PACS,^{6,7} including in never-hospitalised people up to 41 weeks postinfection.⁸ However, longitudinal ¹²⁹Xe 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 ¹²⁹Xe 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 ¹²⁹Xe ventilation MRI, ¹²⁹Xe 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 ¹²⁹Xe 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 participants⁸ 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 ¹²⁹Xe 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
¹²⁹Xe 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

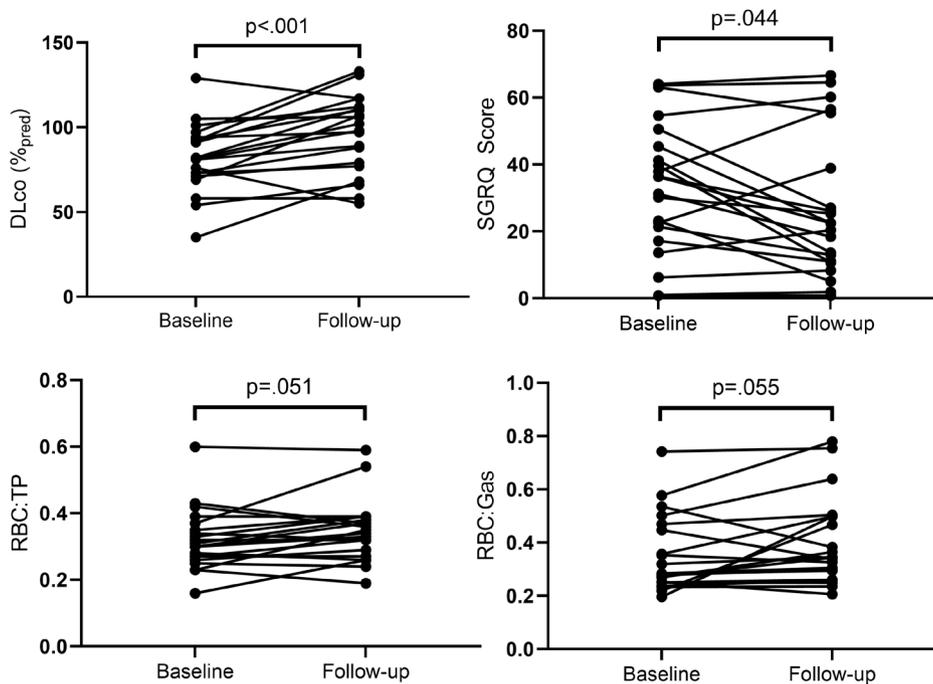


Figure 1 Clinical, quality of life and imaging measurements at baseline (7±4 months since PCR test) and follow-up (14±4 months since PCR test). (A) shows tabulated baseline and follow-up measurements. (B) provides spaghetti plots for DL_{CO}, SGRQ score, ¹²⁹Xe MRI RBC:TP and RBC:gas measurements at baseline 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; FEV₁, 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 ($\Delta=22$; 95% CI=0 to 44, $p=0.084$) and FeNO ($\Delta=-3$; 95% CI=-6 to -1, $p=0.084$) between visits; FeNO measurements were normal across visits. DL_{CO} ($\Delta=14$; 95% CI=7 to 21, $p<0.001$), SGRQ-total ($\Delta=-6$; 95% CI=-1 to -11, $p=0.044$) and symptom-score ($\Delta=-11$; 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, $\Delta=-0.7$; 95% CI=-0.2 to -1.2, $p=0.019$) but not ¹²⁹Xe RBC:TP ($\Delta=0.03$; 95% CI=0.01 to 0.05, $p=0.051$), ¹²⁹Xe RBC:gas ($\Delta=0.06$; 95% CI=0.02 to 0.10, $p=0.055$) or

FeNO ($\Delta=-3$; 95% CI=0 to -6, $p=0.084$) at 14 months. At baseline, two participants desaturated ($\Delta\text{SpO}_2=-9\%$, -7%) following the 6MWT while at follow-up, no participants desaturated.

Figure 2 shows representative three-dimensional ¹²⁹Xe MRI RBC maps coregistered with the corresponding segmented CT vessel tree for a single 31-year-old male participant at baseline and follow-up. ¹²⁹Xe 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

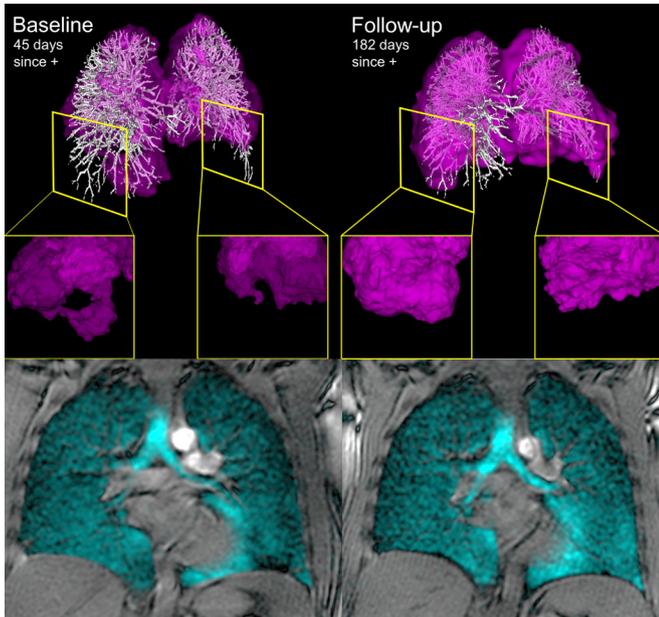


Figure 2 ^{129}Xe MRI and coregistered pulmonary vascular tree CT at baseline and follow-up. Left and right panels show ^{129}Xe MRI RBC map (pink) coregistered with CT pulmonary vascular tree (white) and bottom panels show ^{129}Xe ventilation images (cyan) for a previously healthy participant hospitalised 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 improvements⁹ 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 ($\rho=0.48$, 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, $\rho=0.57$, 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 work⁸ 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

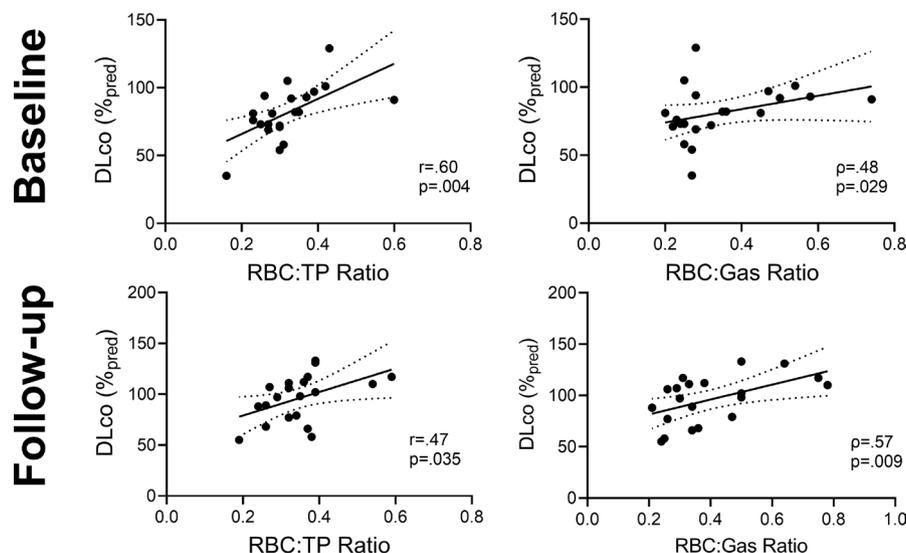


Figure 3 Correlations between DL_{CO} and ^{129}Xe MRI measurements. At baseline and follow-up, there were weak to moderate, significant correlations between DL_{CO} and ^{129}Xe MRI RBC:TP and RBC:gas ratios. (Participants with DL_{CO} measurement $n=20$). DL_{CO} , diffusing capacity of the lung for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

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 ¹²⁹Xe gas-transfer MRI study of PACS. This study was limited by small sample size. ¹²⁹Xe 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 Cyclomedica, 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.

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