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EXPLAIN [COV-LT2-0049]

Title: HypErpolarised Xenon Magnetic Resonance PuLmonary ImAging In PatieNts with Long-COVID

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Plain English Summary

Post-COVID-19 condition, or Long Covid, causes a wide range of symptoms but fatigue, brain fog and breathlessness are most common. The reason for symptoms remains poorly understood but is likely to be complicated and may differ between individuals. In this study, we were interested in understanding why breathlessness is such a common symptom in patients who were not hospitalised during their infection.

Our study used a state-of-the-art technique called Hyperpolarised Xenon MRI (HPX-MRI) to look at the lungs of patients struggling with breathlessness after COVID-19. The technique involves breathing in a gas called xenon whilst lying in an MRI scanner. This type of scan has been used to study different lung diseases and has also been used in breathless patients following hospital admission with COVID-19. These studies have found that HPX-MRI is an extremely sensitive test and is able to detect very small amounts of damage to lungs even when it is normal on CT (Computed Tomography).

We had 3 groups in our study. 1) Breathless Long Covid participants 2) Long Covid participants who were not breathless 3) Controls who had fully recovered from COVID. In addition to HPX-MRI, we performed CT scans, questionnaires, exercise tests and lung function tests. We also looked at markers in the blood to see if there was any detectable abnormality that may increase risk of blood clot formation. Our results showed that the lungs on CT and HPX-MRI were normal in all 3 groups including those who were breathless with Long Covid. We found no evidence of a blood clotting problem.

Executive Summary

Study aims and objectives: The primary objective of this study was to evaluate whether breathlessness in non-hospitalised Long Covid (NHLC) participants was

due to lung damage, as assessed by hyperpolarised 129xenon MRI (HPX-MRI). To do this, we undertook HPX-MRI and contrast perfusion MRI and correlated measurements with traditional lung function tests and symptom-based questionnaires in breathless NHLC participants. We compared the findings to non-breathless NHLC participants and fully recovered post-COVID controls. Secondary objectives were 1) to assess for the presence of ventilation abnormalities in the lungs using ventilation HPX-MRI 2) determine whether there was evidence of coagulopathy or vasculopathy in Long Covid.

Background: Post-COVID-19 condition, or Long Covid (LC) as it is more commonly known, is estimated to affect 2 million people living in the UK. It is characterised by a wide range of symptoms although breathlessness, fatigue and brain fog are most frequently described. The mechanisms driving symptoms are complex, and to date, remain poorly understood.
The severity of initial symptoms do not predict the development of LC and many patients have a relatively mild illness acutely. Hospitalised patients usually have evidence of pneumonic changes on CT scans that can take several months to resolve, and sometimes leave a fibrotic 'footprint' causing persistent lung function impairment and exercise intolerance. In contrast, patients not admitted to hospital rarely have evidence of pneumonia and chest imaging to investigate persistent breathlessness after the infection is usually normal. Despite this, up to 50% of LC sufferers report breathlessness and it can be the main symptom limiting return to functional activity.
HPX-MRI is a state-of-the art imaging modality that is safe, reproducible and quantitative. The MRI-based technique involves the subject breathing in 129xenon, an inert gas that has been hyperpolarised to make it spectroscopically visible using MRI. Xenon mirrors the flow of oxygen through the bronchial tree, across the alveolar membrane and into the pulmonary vasculature. Disruptions in the passage of xenon due to ventilation, diffusion or perfusion abnormalities can be both visualised and quantified. Functional measurements of gas exchange within regional areas of the lung can be obtained that are not identifiable using global measures such as the Transfer factor for Carbon Monoxide (TLCO). We previously reported. HPX-MRI findings of patients hospitalised with COVID-19 and found that at 3 months, the majority had significant functional abnormalities despite having near normal CT scans. Furthermore, when we undertook HPX-MRI on first-wave non-hospitalised patients with breathlessness, we found similar findings. 7 of 11 (63%) patients had abnormal HPX-MRI measurements but normal CTs.
The main aim of this study was to see if these initial findings were replicated in a larger cohort of LC sufferers. We wanted to see if the abnormalities observed were seen in breathless patients or in all patients with Long Covid, including those with fatigue-predominant presentations without breathlessness. Furthermore, we wanted to see if the abnormalities observed were specific to those with Long Covid or whether they also existed in individuals who had fully

recovered from COVID. By including non-breathless Long Covid participants and those who had fully recovered from COVID, we reasoned that we would be able to determine whether the presence of functional abnormalities detected by HPX-MRI was the cause of breathlessness or an incidental finding.

Methods: This was a prospective, observational, multi-centre cohort study enrolling non-hospitalised Long Covid (NHLC) patients from 4 dedicated post-COVID centres in the UK between the 27th May 2022 to December 31st 2023. Participants recruited into the study included those who developed LC following infection during the first wave of the pandemic and thereafter. All study participants had symptoms for a minimum of 3 months and those with other causes for symptoms were excluded prior to enrolment. The diagnosis of LC plus the presence or absence of breathlessness was determined by the clinician at the time of the clinic appointment.
HPX-MRI was undertaken at Oxford and Sheffield study sites. Participants had a chest CT within a month of MRI. Clinical data was collected prospectively and comprised demographics, symptom-based questionnaires, pulmonary function tests (PFTs), blood sampling and a 1-minute-sit-to-stand test (STST). Patients who had abnormal lung imaging (score ≥5) were excluded. Pregnancy, uncontrolled asthma, smoking history >10 pack years and clinically significant cardiorespiratory pathology were also exclusions. Control participants formed 2 groups: 1) NHLC with typical symptoms but without breathlessness 2) Participants who had had COVID infection and fully recovered. Controls underwent PFTs, chest CT and HPXMRI.
Plasma and urine samples were obtained. Mediators representative of coagulopathy, platelet activation, endothelial activation and neutrophil activation were measured using ELISA. The presence, size and quantity of microaggregates ('microclots') was assessed using immunofluorescence and confocal microscopy (analysis in progress).

Results: 275 participants were enrolled into the study. 247 were scanned and 223 had satisfactory HPX-MRI results. Of these, 121 were breathless (BLC), 51 non-breathless (NBLC) and 49 were controls. Groups were well matched for age, gender, BMI and ethnicity. Fatigues and anxiety scores (FACIT-F, GAD-7) were similar between BLC and NBLC. Breathlessness scores measured using Dyspnoea-12 and modified BORG dyspnoea score were significantly higher in the BLC group (both p=<0.001). STST repetitions was reduced in BLC and NBLC compared to controls (p=<0.001). FEV1 and FVC were reduced in the BLC group compared to NBLC and controls (p=0.040, p=0.013 and p=0.042 and p= 0.046, respectively). TLCO was reduced in BLC compared to NBLC and controls (p=0.026, p<0.001) but when corrected for alveolar volume, the KCO was not significantly different between BLC and NBLC. The majority of lung function values were within internationally standardised normal ranges in all groups. HPX-MRI revealed no evidence of diffusion abnormalities demonstrated by the

red blood cell to membrane ratio (RBC:M) between the 3 groups. HPX-MRI analysis looking at RBC:M in the lower, middle and upper lungs to assess regional abnormality did not differ between the groups. There were no differences in the contrast-enhanced perfusion parameters or the proportion and extent of ventilation defects. Plasma biomarkers representative of coagulopathy (D-dimer, fibrinogen), fibrinolysis (soluble thrombomodulin, PAI-1), platelet activation (p-selectin, sCD40L, 11-dehydro-thromboxane-B2), endothelial activation (vWF antigen) and neutrophil activation through NETosis (myeloperoxidase, citH3) were not significantly different between BLC, NBLC and controls.

Key findings: Pulmonary function tests reveal slightly lower values in breathless LC participants although the majority of these participants had PFT values within normal range.
Using HPX-MRI, we found no evidence of global or regional lung abnormalities in breathless LC participants compared to controls. This included analysis of the RBC:M, (reflecting the integrity of alveolar-capillary membrane), pulmonary blow flow and mean transit time (reflecting pulmonary vascular perfusion) or percentage of ventilation defects (reflecting areas of airways narrowing). We have found no evidence of a hypercoagulable state or vasculopathy in LC participants compared to controls although final analysis of microclot data is awaited.

Conclusions and recommendations for future work: Breathlessness is a common and sometimes distressing symptom in LC. The mechanisms driving breathlessness have not been established although early work suggested persistent lung damage may be an explanation in some patients. Using state-of-the-art imaging to probe the functionality of the lungs, we found no evidence of diffusion, perfusion or ventilatory abnormalities in the lungs of LC participants. Furthermore, we found no evidence to support the hypothesis that LC is caused by vascular abnormalities or coagulopathy. This is the largest study to date to investigate breathlessness in Long Covid and the results appear to indicate that it is not due to abnormalities or damage within the lungs. Future directions to investigate breathlessness in LC should focus outside the lungs, in particular how altered breathing patterns can contribute to breathlessness and exercise intolerance.

Dissemination plans: The results from this study have been presented at international conferences and are in the process of submission to peer-review journals.

Expected influence/impact: Although this is a negative study, we believe that these findings will have significant impact and influence on clinical practice. Breathlessness in Long Covid can be frightening and limit return to functional

activity. There is often a fear that breathing difficulties are the result of hidden lung damage, driven in part by early pandemic data demonstrating persisting lung abnormalities in patients after COVID pneumonia. Although hospitalised patients typically represent a distinct demographic group to those not hospitalised, until now, it has not been possible to reassure patients with certainty that their lungs are functionally normal. High-risk and unproven treatments have been sought by patients, including anticoagulation and plasmapheresis. This study demonstrates that the lungs and pulmonary vasculature of non-hospitalised Long Covid patients do not show evidence of concealed pathology. Furthermore, in this well-characterised Long Covid cohort, we have found no evidence of coagulopathy or pulmonary vascular abnormalities providing scientific evidence arguing use of such treatments. The results of this study should reassure clinicians and patients alike that the focus should be around holistic management rather than extensive investigation, with an emphasis on physiotherapy-guided breathing techniques.

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Glossary

BLC	Breathless Long COVID
CT	Computed Tomography
ELISA	Enzyme-Linked Immunosorbent Assay
HPX-MRI	Hyperpolarised Xenon MRI
NBLC	Non-Breathless Long Covid
NHLC	Non-Hospitalised Long Covid
PFTs	Pulmonary Function Tests

Key Publications

1. K.L. Ng et al (2025) Breathlessness in Long COVID: Exploring the relationship between symptoms, lung function tests, and functional imaging using Hyperpolarised Xenon MRI. *Lancet preprints.*
2. J.H. Pilgrim-Morris et al (2025) A framework for modelling whole-lung and regional transfer factor of the lung for carbon monoxide using hyperpolarised xenon-129 lung magnetic resonance imaging. *ERJ Open Research.*
3. K. Yeung et al (2024) Evaluation of an integrated variable flip angle protocol to estimate coil B1 for hyperpolarized MRI. *Magnetic Resonance in Medicine.*
4. G.J. Collier et al (2024) Age, sex, and lung volume dependence of dissolved xenon-129 MRI gas exchange metrics. *Magnetic Resonance in Medicine.*

5. **M. Kim et al (2024)** Functional Impairment in Small Airways Associated With the Breathlessness Symptoms in Long Coronavirus Disease. *J Thorac Imaging.*
6. **J.M. Wild et al (2023)** Review of Hyperpolarized Pulmonary Functional 129 Xe MR for Long-COVID. *J Magn Reson Imaging.*
7. **L.C. Saunders et al (2023)** Longitudinal Lung Function Assessment of Patients Hospitalized With COVID-19 Using 1H and 129Xe Lung MRI. *CHEST Journal.*
8. **I. Stewart et al (2023)** Residual Lung Abnormalities after COVID-19 Hospitalization: Interim Analysis of the UKILD Post-COVID-19 Study. *Am J Respir Crit Care Med.*
9. **O. Doganay et al (2023)** Gas exchange and ventilation imaging of healthy and COPD subjects using hyperpolarized xenon-129 MRI and a 3D alveolar gas-exchange model. *European Radiology.*
10. **C.P. Kotanidis et al (2022)** Constructing custom-made radiotranscriptomic signatures of vascular inflammation from routine CT angiograms: a prospective outcomes validation study in COVID-19. *Lancet Digit Health.*
11. **J.M. Wild et al (2022)** Understanding the burden of interstitial lung disease post-COVID-19: the UK Interstitial Lung Disease-Long COVID Study (UKILD-Long COVID). *BMJ Open Respir Res.*
12. **J.T. Grist et al (2022)** Lung Abnormalities Detected with Hyperpolarized 129Xe MRI in Patients with Long COVID. *Radiology.*
13. **F. Gleeson & E. Fraser (2022)** Hyperpolarized Xenon MRI, Further Evidence of Its Use in Progressive Pulmonary Fibrosis? *Radiology.*
14. **S. Inui et al (2022)** Impaired pulmonary ventilation beyond pneumonia in COVID-19: A preliminary observation. *PloS One.*
15. **J. Bewes et al (2021)** Imaging Dynamic Expiration: Feasibility of MRI Spirometry Using Hyperpolarized Xenon Gas. *Radiology Cardiothoracic Imaging.*
16. **M. Kim et al (2021)** Lobar Ventilation in Patients with COPD Assessed with the Full-Scale Airway Network Flow Model and Xenon-enhanced Dual-Energy CT. *Radiology.*
17. **J.T. Grist et al (2021)** Hyperpolarized 129Xe MRI Abnormalities in Dyspneic Patients 3 Months after COVID-19 Pneumonia: Preliminary Results. *Radiology.*