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Step on the ^{129}Xe Gas: The MRI Race to Uncover Drivers of Post-COVID-19 Symptoms

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Grace Parraga and Alexander M. Matheson

G Parraga PhD, FCAHS Professor, Department of Medical Biophysics, Division of Respirology Department of Medicine, Western University gparraga@robarts.ca
AM Matheson BSc, Department of Medical Biophysics, Western University amathe57@uwo.ca

Correspondence to: Grace Parraga PhD FCAHS
Room 5235
Robarts Research Institute
Western University
1151 Richmond St N
London Canada
N6A 5B7
gparraga@robarts.ca

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See also the article by Grist et al.

Following COVID-19 infection, symptoms may persist in patients for long periods of time, which in some cases, has a tremendous impact on quality-of-life.[1] The American Centers for Disease Control and Prevention (CDC) coined the term ***post-COVID condition*** to help explain such persistent symptoms defined as "a wide range of new, returning, or ongoing health problems people can experience *four or more weeks* after first being infected with COVID-19."[2] The World Health Organization (WHO) also developed a consensus definition for the ***post-COVID-19 condition*** as: "usually *three months* from the onset of COVID-19 with symptoms that last at least two months."[3] Alternatively***, post-acute sequelae of COVID-19*** was also defined as symptoms in those people who survived at least the first 30 days following a COVID-19 diagnosis.[4] Finally, the National Institute for Health and Care Excellence coined the term ***long-COVID*** to describe the signs and symptoms that continue or develop from 4 to 12 weeks following the acute infectious phase of COVID-19.[5]

Regardless the confusing nomenclature and emerging definitions, such symptoms in patients can vary considerably, with fatigue, dyspnea, exercise limitation, exertional dyspnea, chest pain, and brain fog, most commonly reported.[1,6] In ever-hospitalized post-COVID-19 patients, chest CT has revealed fibrotic lung abnormalities which may be partially responsible for respiratory symptoms.[1] However, and uninformatively, symptomatic post-COVID-19 patients typically report normal pulmonary function tests [6,7] and in some cases, normal or very mildly abnormal diffusing-capacity-of-the-lung-for-carbon-monoxide.[7] Hence, and unfortunately, the pathophysiological drivers of post-acute COVID-19 symptoms are not well-understood, which makes treatment decisions difficult, if not impossible.

In an effort to understand the underlying cause of post-COVID-19 symptoms and limitations, two recent pilot studies harnessed the unique strengths of hyperpolarized ^{129}Xe MRI to investigate two

small groups of participants from Wuhan[8] and Oxford UK,[9] respectively. Hyperpolarized ^{129}Xe MRI pulmonary measurements are driven by the unique properties of inhaled ^{129}Xe gas, which in the healthy human lung instantaneously fills the terminal bronchi and lung parenchyma, participates in transmembrane diffusion through the alveolar-capillary membranes and binds to red blood cells (RBC) in the pulmonary capillaries. This novel pulmonary functional imaging method provides a way to non-invasively and simultaneously capture a subvoxel snapshot in time of inhaled gas delivery, flow, diffusion and RBC binding throughout the entire lung.

Both previous studies evaluated recently discharged COVID patients[8,9] and reported abnormal ^{129}Xe MRI RBC to alveolar tissue barrier ratios which suggested persistently abnormal oxygen and carbon dioxide gas-exchange. These initial studies did not interrogate post-COVID-19 patients who had never been hospitalized, nor did they evaluate the relationship of ^{129}Xe MRI findings with symptoms including dyspnea and exercise limitation. Moreover, whether the measured gas-exchange abnormalities represented a general post-COVID condition or were due to other COVID complications such as pulmonary embolism or other coagulopathies post-hospitalization, was not ascertained. While the results of both studies were consistent and illuminating, they did not answer a number of lingering but important questions: *Do never-hospitalized post-COVID-19 patients who experienced less severe infection also have gas-exchange abnormalities? Do ^{129}Xe MRI findings of abnormal gas-exchange track with, or explain enduring COVID-19 symptoms including exercise limitation, dyspnea and post-exertional dyspnea?*

In this issue of *Radiology*, Grist and colleagues based at Sheffield and Oxford in the UK **(CITE)** answer some of these remaining questions. They evaluated ^{129}Xe MRI measurements of the pulmonary RBC:barrier ratio as a surrogate of abnormal gas-exchange in a small group of contemporaneous ever- and never-hospitalized participants with symptoms consistent with long-

COVID. Thirty-six patients were enrolled including 11 never-hospitalized (NHLC), 12 previously hospitalized COVID participants (PHC) and 13 healthy volunteers who had not been infected. Post-COVID participants were recruited on the basis of unexplained dyspnea and with normal or near-normal chest CT imaging. The authors reported significantly lower ^{129}Xe MRI RBC:barrier ratio in both NHLC and PHC subgroups compared to healthy volunteers, but there was no difference between NHLC and PHC measurements, with the time to follow-up longer in the NHLC subgroup (287 ±79 days versus 143 ±72 days respectively). In addition, there were no differences in spirometry measurements between the two subgroups and mean DL_{CO} was normal but significantly lower in the NHLC versus PHC subgroup. Regardless of these differences, the take home message is clear: *you don't need to have been hospitalized with a severe COVID-19 infection to suffer long term symptoms and abnormal MRI gas-exchange measurements. Moreover, even if spirometry, DL_{CO} and chest CT are normal, symptoms and ^{129}Xe MRI gas-exchange abnormalities persist for long periods of time post-infection.*

This important study expanded on previously published ^{129}Xe MRI COVID-19 work[8] by focusing on ever- and never-hospitalized participants and examining relationships between ^{129}Xe and clinical measurements. Importantly, the authors also observed a relationship between RBC:barrier and DL_{CO} in both NHLC and PHC groups. Similar findings have been previously reported in patients with idiopathic pulmonary fibrosis,[10] suggesting that RBC:barrier provides a surrogate measure of gas-transfer. In addition, here the ^{129}Xe MRI RBC:barrier ratio and dyspnea (Dyspnea-12 and modified BORG scale) trended towards an association (P=.06 and P=.08), which speaks to a potential relationship between these symptoms and MRI measurements.

Despite abnormal MRI measurements in post-COVID-19 participants, CT images were normal or only modestly abnormal. While CT has superior spatial resolution, here the ^{129}Xe MRI signal was

generated at the alveolar level and averaged over an entire voxel, effectively allowing ^{129}Xe MRI to probe abnormalities with subvoxel, alveolar membrane spatial resolution. Therefore, it is not surprising that ^{129}Xe MRI may be sensitive to functional abnormalities not observed structurally on CT. Whether the ^{129}Xe MRI RBC:barrier ratio is similarly impaired in the presence of fibrosis should be studied further.

Limitations included the small sample size which likely resulted in an inability to measure significant relationships between the novel MRI measurements and symptoms or exercise limitation, which is a pity. In addition, future studies ought to consider larger sample sizes with a longitudinal component because it is still difficult to be certain about the pre-COVID lung health of the patients studied here.

Previous ^{129}Xe MRI studies focused on ever-hospitalized post-COVID-19 participants which limited our understanding of the post-COVID condition to those with the most severe disease. Alarmingly, here Grist and colleagues reported that both PHC and NHLC participants had significantly lower MRI RBC:barrier ratio compared to healthy volunteers. This important finding tells us that even mild disease can result in persistent symptoms and gas-exchange differences. An exact timepoint at which COVID infection may resolved is still a matter of debate, however here data in never-hospitalized participants was acquired at least six months following infection. It is therefore unlikely that these changes were due to residual infection, and more likely they reflect temporally persistent gas-exchange abnormalities that stem from the pulmonary vasculature or alveolar membrane.

Taken together, these results emphasize the power and sensitivity of pulmonary functional imaging and the fact that gas-exchange abnormalities that stem either from the alveolar membrane or pulmonary vasculature may be important pathophysiological drivers of symptoms in post-COVID-

19 patients. Moreover, Grist and colleagues reported MRI gas-exchange findings that were beyond the sensitivity of pulmonary function tests including DL_{CO} and were not flagged as obvious abnormalities in chest CT images either.

The COVID-19 pandemic has provided unprecedented challenges and important opportunities to better understand the natural history of viral lung infection in millions of patients. These hyperpolarized ^{129}Xe MRI findings reveal new valuable clues about lung abnormalities that endure, months post-infection, perhaps putting post-COVID patients back in the driver's seat of their recovery.

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Grace Parraga PhD FCAHS is a Professor in the Department of Medical Biophysics, Division of Respirology, Department of Medicine and Robarts Research Institute, all at Western University, London, Canada. She is the recipient of a Tier 1 Canada Research Chair and her laboratory focuses on providing a deeper understanding (via non-invasive pulmonary imaging) of chronic lung disease initiation, progression, and response to therapy. Her laboratory is currently home to ~20 trainees and staff, and she has trained over 200 students and fellows in the past 15 years.

Alexander Matheson, BSc is a PhD candidate in the Department of Medical Biophysics at Western University, London, Canada. He holds a Natural Sciences and Engineering Research Council (Canada) Alexander Graham Bell Canada Graduate Scholarship. His research focuses on developing CT and MRI biomarkers of vascular pathophysiology in chronic lung diseases such as asthma, chronic obstructive pulmonary disease and post-acute COVID-19 syndrome.