

^{129}Xe Pulmonary MRI for Individuals with Post-acute COVID-19 Syndrome

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There has been considerable effort put into understanding why certain patients have ongoing symptoms of breathlessness after acute COVID-19 disease. Efforts to understand this aspect of so-called “long COVID” have focused on functional and structural lung imaging.

Several studies with contrast-enhanced and dual-energy CT have assessed chronic pulmonary vascular perfusion deficit in acute COVID-19 lung disease (1–3). However, such studies have tended to focus on patients with severe and acute lung disease diagnosed with use of CT. The ability of the CT perfusion methods clinically used to quantify and resolve microvascular capillary perfusion deficits can be limited, especially where there is no structural abnormality seen at lung CT (4).

Unique pulmonary functional information can instead be evaluated by use of inhaled hyperpolarized xenon ^{129}Xe MRI. This method tracks the passage of xenon along the oxygen uptake path in the lungs (5). With spectroscopic imaging of ^{129}Xe gas transfer, xenon gas can be measured in the ventilated alveoli, dissolved in the interstitial tissue, and, finally, taken up by the red blood cells (RBCs) in the capillaries. ^{129}Xe gas-transfer MRI is very sensitive to early lung pathophysiologic conditions and disease progression in interstitial lung diseases (6,7). The method is being used in the clinical setting to

understand why some patients present with unexplained breathlessness (8). The method has recently been applied to understand the pathophysiology of acute COVID-19 lung disease in China (9) after hospital discharge. In the United Kingdom, ^{129}Xe MRI has highlighted regional physiologic deficits in gas transfer in patients with post-COVID-19 breathlessness, despite the absence of structural abnormality at CT (10).

In this issue of *Radiology*, Matheson and colleagues (10) demonstrated abnormalities in dissolved xenon uptake in the RBCs in the capillaries and link this with evidence of small vessel pruning from quantitative analysis of CT in the lungs. Their study was performed in a group of patients with post-acute COVID-19 lung symptoms (12 hospitalized and 22 non-hospitalized). Matheson et al (10) demonstrated that in symptomatic patients with post-acute COVID-19 syndrome (PACS), ^{129}Xe gas-exchange MR spectroscopy and CT vascular density metrics were abnormal and related to lung function tests (diffusion capacity of carbon monoxide and forced expiratory volume in 1 second) and symptoms of exercise limitation and dyspnea.

Matheson et al (10) are to be commended for linking the CT vascular and xenon gas-exchange modalities and for systematically performing lung function tests in these patients. The evidence here suggests that the perceived xenon deficit in the RBC signal may be caused by microvascular abnormality rather than interstitial diffusion limitation. Without wanting to detract from this timely work from our respected colleagues, there are a couple of points worth noting.

First, the quantitative findings presented are derived from global ^{129}Xe lung MR spectroscopy (eg, the ratio of the spectral peaks from the RBCs and the tissue membrane and the area under these spectral peaks). This in itself is fine, but it would be good to see some analysis of the xenon images that are depicted in the article. Of real interest would be an analysis of the regional heterogeneity of the xenon gas-transfer MRI metrics alongside the regional vessel analysis from CT. Moreover, the values of the area under the individual spectral peaks also need to be treated with a bit of caution as they are not normalized for system- and/or subject-dependent factors (see the abundant hydrogen-proton nuclear MR spectroscopy literature where ratios or external reference signals are still routinely used). An example of one such factor for xenon MR spectroscopy is the inhaled xenon concentration (gas dose per lung volume); here, all subjects received a fixed dose of 1 L of gas, irrespective of their lung volume.

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Conflicts of interest are listed at the end of this article.

See also the article by Matheson et al in this issue.

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Second, there was a substantial difference in age between the healthy and patient cohorts, which makes it hard to interpret the differences between the groups. The authors mention this and state there is no literature out yet on age dependence of xenon gas-transfer MR indexes, but recently, both the Duke and Sheffield groups independently reported that the RBC:barrier ratio decreases by 0.04 with every 10 years of age. The age difference between the groups reported here is on average 18 years; as such, we should expect the RBC:barrier ratio for healthy controls to drop from 0.41 to 0.35 if corrected for age, which is what is being reported here for the patient group with PACS.

We are pleased to see this work adding to the literature on dissolved xenon MRI in post-COVID-19 lung disease and share the sense of urgency to understand post-COVID-19 lung symptoms. We do, however, need to make sure that the findings sit sensibly with appropriately age-matched normative data before clinically meaningful conclusions can be drawn. As investigators in this area, we are committed to this, and it would be interesting to see a pooling of benchmarked normative data. In further work, it would also be of serious interest to follow up on this detailed patient cohort study and see if the perceived gas-transfer abnormality from xenon MRI improves alongside the lung function, vascular CT, or complementary dynamic contrast-enhanced lung-perfusion MRI methods that can help quantify microvascular capillary perfusion abnormality.

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