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Detecting COVID-19-related Chronic Pulmonary Injury with ^{129}Xe MRI

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See also the article by Grist et al.

Abbreviations

ppm = parts per million

RBC = red blood cell

TP = tissue and plasma

The ongoing COVID-19 pandemic poses many new, unprecedented demands on healthcare systems. The demand for radiological diagnosis of associated pulmonary injury is of particular interest (1). First-line imaging modalities in COVID-19 pneumonia are chest x-ray and CT (2). But there is growing interest in MRI for the assessment of post-COVID-19 symptoms (Long COVID) of the lungs (3).

Proton-based (^{1}H) MRI of the lungs at 1.5 or 3 T is difficult. The heterogeneous microstructure of the lung tissue causes low proton density of the lung parenchyma and very short T2* relaxation time constants. Newer lung MRI techniques can avoid some of these issues by using ultrashort echo times to improve the structural depiction of the lung (4).

However, to obtain more information about ventilation and lung function, including pulmonary gas transfer, other MRI techniques are preferred. These include oxygen-enhanced lung MRI, Fourier-decomposition lung MRI, fluorine-19 MRI, and, in particular, lung MRI with hyperpolarized noble gases (5). In the latter, the MRI signal is no longer based on spinning protons (hydrogen nuclei) but on the detection of atomic nuclei of helium (^{3}He) or xenon (^{129}Xe) gas. A particular challenge of these gas-based MRI techniques is that the physical and spin density of gases is lower (roughly by a factor of 1000) than the proton density of biological tissue. Thus, without special amplification techniques, the MRI signal of noble gases is also several orders of magnitude lower. Fortunately, this signal can be substantially improved by a physical process called hyperpolarization: In conventional MRI, the fraction of protons that is aligned with the external magnetic field and contributes to the MRI signal is only about 0.001 % (the so-called thermal polarization of protons at 3 Tesla). Using an external device known as a polarizer, this fraction can be artificially boosted to roughly 10 % or more for helium and xenon gas. After hyperpolarization, the gas is administered (by inhalation) to patients in the MRI scanner. This gas intake results in an increase of MRI signal intensity by a factor of about 10,000, which more than compensates for the low intrinsic spin density. Of note, on the cost side of hyperpolarized MRI are considerable

investments in dedicated hardware. These costly investments include receive coils (tuned to the Larmor frequency of e.g. the isotope xenon-129) as well as the gas polarizing equipment.

After administration of the hyperpolarized gas, xenon-129 (^{129}Xe) MRI provides an immediate depiction of the regional ventilation of the lung by showing the spatial distribution of the inhaled gas (6). However, ^{129}Xe MRI can do more than ventilation imaging. Xenon partially dissolves in the lung tissue, the blood plasma, and in the erythrocytes. Thus, Xenon mimics oxygen transfer in the lungs, and ^{129}Xe MRI can detect and quantify the pulmonary gas transport from the alveoli to the blood. To do so, the spectroscopic properties of the ^{129}Xe MRI signal are exploited to differentiate xenon contributions from the various physiological compartments.

Inhaled xenon-129 exhibits three different Larmor frequencies located at 0 ppm, 197 ppm, and 217 ppm. The frequency of xenon in the gas phase is used as reference value at 0 ppm. The Larmor frequency of xenon dissolved in lung tissue or plasma (TP compartment, sometimes referred to as the “barrier”) is shifted by about 197 ppm relative to that of xenon gas. Xenon in red blood cells (RBC compartment) is shifted by about 217 ppm. Only a small fraction (1 to 2%) of the inhaled xenon is dissolved in the lungs. But it is possible to perform chemical-shift imaging of each of these three contributions (gas phase, TP, and RBC compartment) using techniques analogous to fat-water separation in e.g. Dixon MRI. Thus, the spatial signal intensity and distribution of xenon in these three compartments can be separately extracted and reconstructed. The assessment of pulmonary function and gas exchange using the RBC-to-TP signal ratio of the xenon signal in erythrocytes relative to the signal in tissue and plasma is of particular interest. The RBC-to-TP signal ratio strongly correlates with the diffusing capacity of the lungs for carbon monoxide (DLCO), as assessed in idiopathic pulmonary fibrosis (7). It is also possible to quantify the spectral widths of the frequency peaks in hertz (Hz). These spectral widths of the peaks are hypothesized to correlate with oxygenation properties and the thickness of the interstitial barrier tissue (7).

In this issue of *Radiology*, Grist et al. (8) present preliminary results of a prospective study in nine participants examined and scanned with ^{129}Xe MRI between 3 and 8 months after hospital discharge following COVID-19 infection. All study participants had been tested positive for SARS-CoV-2 but did not receive invasive ventilation during hospitalization. Five healthy volunteers (controls) without history of SARS-CoV-2 infection were scanned with the same ^{129}Xe MRI protocol. The ^{129}Xe MRI pulse sequence used was a 3D 4-echo radial acquisition recently described in healthy volunteers and patients with idiopathic pulmonary fibrosis (9). This approach can acquire spatial distribution maps of dissolved xenon in the lungs with an isotropic resolution of 1.75 cm.

For the ^{129}Xe MRI results, the authors report differences of the RBC-to-TP ratio ($p = .001$) between participants following COVID-19 infection (0.3 ± 0.1) and healthy controls (0.5 ± 0.1). The authors also report differences between participants and controls in the spectral widths of the RBC frequency peaks and xenon gas frequency peaks (median: 507 ± 81 vs 567 ± 1 Hz, $p = .002$ and 122 ± 17 vs 104 ± 2 Hz, $p = .004$, respectively). In particular, the reduced RBC-to-TP ratio of the xenon signal intensity in the red blood cells relative to the tissue/plasma signal intensity indicates compromised gas exchange in the lung. Interestingly, the post-COVID-19 participants had normal or near normal CT results and normal DLCO results (available in 7 out of 9 participants) at the time of the ^{129}Xe MRI scan. Medical Research Council breathlessness scale and modified BORG dyspnea scores were higher (up to 2 of 5 and 3 of 10, respectively) in six of the nine participants. The authors conclude from these results that ^{129}Xe MRI "appears to provide an explanation for participant symptoms not explained by other clinical data or imaging techniques" and that "hyperpolarized xenon MRI may be a potentially useful imaging modality in dyspneic participants with Long-COVID." (8)

The reported results are promising with respect to assessment of patients with chronic post-COVID-19 symptoms. They are also in line with a 2021 report of ^{129}Xe MRI findings in participants with COVID-19

examined less than a month after discharge (10). However, the current results also require careful interpretation due to several limitations of both the study design and the cohort characteristics. First, both examined groups were very small (n = 9 patients, 5 controls). The post-COVID-19 participants were 57 ± 7 years old and predominantly men (6 out of 9). In contrast, the control group was much younger (29 ± 3 years) and only women. No larger studies are available that quantify how ^{129}Xe MRI parameters, such as the RBC-to-TP ratio, depend on age or sex. Thus, it is difficult to differentiate between the influence of age and of potential COVID-19-related changes. A second important limitation is that the participant recruitment strategy was not based on persisting COVID-19-related symptoms, such as breathlessness. Thus, the post-COVID-19 participants present without or with mild dyspnea but not with consistent unambiguous or severe Long COVID symptoms. Therefore, it is a risk to draw any conclusions about the value of ^{129}Xe MRI in participants with Long COVID based on the included participants in this study.

Ultimately, further study of ^{129}Xe MRI in Long COVID requires larger studies and better defined participant groups. Ideally, at least three sufficiently large groups should be compared using ^{129}Xe MRI: healthy controls without a history of COVID-19, participants who fully recovered from COVID-19 without any persisting symptoms, and participants who still experience Long COVID sequelae. The preliminary results by Grist et al. strongly suggest that such studies will substantially improve our knowledge about the causes and diagnosis of post-COVID-19 symptoms.

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