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REVIEWS AND COMMENTARY • EDITORIAL

# Ventilation Defects at $^{129}$Xe MRI in Postacute COVID-19 Syndrome: Back to Normal after 1 Year?

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Postacute COVID-19 syndrome (PACS), increasingly referred to as post–COVID-19 condition, is now recognized as a complex systemic disease that is associated with substantial morbidity. Most patients will recover spontaneously or after acute-phase management, but clinicians and some patients are now faced with long-term complications. PACS is characterized by persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of symptoms. These symptoms are frequently seen and not limited to those patients who have experienced the most severe forms of COVID-19 (1–3).

Dyspnea is the most frequently reported respiratory symptom after COVID-19 infection. Studies reporting respiratory symptoms 1–12 months after COVID-19 show a prevalence of persistent dyspnea ranging from 5% to 81% after hospitalization and approximately 14% in nonhospitalized patients with mild COVID-19 (2,4).

In this issue of *Radiology*, Kooner et al (5) investigate the link between improved airway dysfunction and dyspnea and exercise capacity improvements over time in persons with PACS. The authors hypothesized that in these individuals, xenon 129 ($^{129}$Xe) MRI ventilation defect percentages (VDPs) and quality-of-life scores would significantly improve 12 months from a baseline 3-month follow-up after COVID-19 infection. Kooner et al studied 53 individuals at two centers. In all participants with PACS, forced expiratory volume in 1st second of expiration ($FEV_1$) (mean percent predicted, 84% ± 21 [SD] vs 90% ± 19; $P = .001$), diffusing capacity of the lung for carbon monoxide (DLCO) (mean percent predicted, 86% ± 21 vs 99% ± 22; $P = .002$), St George Respiratory Questionnaire (SGRQ) score (mean, 35 ± 19 vs 25 ± 20; $P < .001$), and VDP (mean, 5.8% ± 7.7 vs 4.2% ± 6.8; $P = .003$) improved between the 3-month and 15-month visit. Furthermore, they showed that VDP measured 3 months after COVID-19 predicted the change in the 6-minute walk distance (a measure for aerobic capacity and endurance) at 15 months (β = -0.643, $P = .006$). In addition, changes in DLCO (β = -0.463, $P = .02$) and forced vital capacity (β = -0.395, $P = .04$) explained the change in SGRQ score.

I congratulate Kooner and colleagues (5) for showing improvements in lung function in persons with PACS 15 months after COVID-19 infection, determining that VDP at 3 months is a predictor for the 6-minute walk distance at 15 months, and linking DLCO and forced vital capacity changes to quality-of-life changes. Without diminishing the scientific success achieved by our respected colleagues, there are some points worth mentioning.

The authors stated that the mean VDP at 15 months (4.2% ± 6.8) remained greater (worse) than the mean VDP values determined in a previously described healthy subgroup (mean age, 36 years; $n = 9$) that never had COVID-19 (1.1% ± 0.9) (6). If one takes a closer look at Table S5, the subgroup without prior respiratory disease (mean age, 52 years; $n = 31$) showed a mean VDP of 1.5% ± 1.1 15 months after COVID-19 infection, which is not notably different than that in the previously reported and much younger healthy subgroup that never had COVID-19. The higher VDP values at 15 months in the study by Kooner et al (5) derive mainly from the subgroup with prior lung disease (mean VDP, 7.4% ± 9.1). Therefore, one could conclude that individuals with PACS without prior lung disease in the reported cohort had regained normal regional ventilation as assessed with $^{129}$Xe MRI 15 months after COVID-19 infection. Also, the mean percent predicted $FEV_1$ (97% ± 11) and mean percent predicted DLCO (105% ± 22) normalized in this subgroup, suggesting adequate ventilation and gas exchange at the alveolar membrane level for age. This would have been great news; however, the mean lung clearance index (no. of breaths, 8.8 ± 1.5), mean modified Medical Research Council dyspnea score (1 ± 1), and mean SGRQ score (21 ± 21) remained slightly abnormal in participants without known lung disease with PACS. These findings may indicate persisting mild small airway changes, dyspnea with mild exercise, and reduced quality of life 15 months after COVID-19 infection. This led the investigators to conclude that there is a complex relationship or link between exercise intolerance and quality of life with MRI, CT, and oscillometry measurements of airway dysfunction. Indeed, PACS is recognized as a multifactorial multisystem complex disease frequently observed to manifest as persistent diverse neurologic, respiratory, or cardiovascular symptoms (2).

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

See also the article by Kooner et al in this issue

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MRI may also help track the passage of hyperpolarized $^{129}$Xe gas along the oxygen uptake path in the lungs. 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 in the capillaries (7). Unfortunately, Kooner et al (5) did not perform any $^{129}$Xe gas-exchange MRI measurements. This would have been valuable to shed more light on the alveolar membrane and capillary functional component of the complex mechanisms and long-term outcome in persons with PACS. Recently, the investigators reported on a small single-center group of 21 participants (mean age, 56 years; seven female) with PACS and persistently abnormal $^{129}$Xe MRI red blood cell–to–tissue plasma ratio values 14 months after infection compared with baseline (7 months after COVID-19 infection). However, the participants also showed significantly normalized levels of percent predicted $D_{LCO}$ in the same observation period (8). In addition, in a prospective study of 11 participants, Grist et al (9) reported significant differences in mean red blood cell–to–tissue plasma ratio values between healthy volunteers and posthospitalized participants with post–COVID-19 condition and nonhospitalized participants with post–COVID-19 condition 5–9 months after COVID-19 infection, despite the presence of normal CT findings. This may indicate a persistent alveolar membrane and capillary functional impairment in persons with PACS. The underlying mechanisms of lung injury in COVID-19 pneumonia are likely due to viral injury and the immune response that the virus generates (10).

Is $^{129}$Xe MRI–derived VDP then back to normal 15 months after COVID-19 infection in patients with PACS? I think this study supports the answer: generally, yes, it is likely back to pre–COVID-19 infection levels. However, regional ventilation is only one aspect of this multifactorial multisystem complex syndrome with a quite variable time course. Therefore, larger multidimensional studies are needed to shed more light on long-term complications (after 12 months) in patients with PACS.

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