Hyperpolarized ^{129}Xe MRI is sensitive to variations in gas exchange impairment in patients with long haul COVID-19 and normal cardiac structure and function

David Mummy, PhD[1], Elianna Bier, PhD[2], Junlan Lu, MS[3], Suphachart Leewiwatwong, MS[2], Aryil Bechtel, BS[4], Isabelle Dummer[5], Sakib Kabir, MS[1], Jennifer Korzekwinski, CRC, RT(N), CNMT[1], Katherine Williford, MS[6], Shelby Martindale, AS, CRTT[6], Coral Giovacchini, MD[6], David Shaz, MD[6], Joseph Mammarappallil, MD, PhD[1], Fawaz Alenezi, MD[6], Raymond Kim, MD[6], Bastiaan Driehuys, PhD[1,2,3], Loretta Que, MD[6]

[1]Radiology, [2]Biomedical Engineering, [3]Medical Physics, and [4]Physics, Duke University, Durham NC, United States, [5]Bioengineering, McGill University, Montreal, QC, Canada, [6]Medicine, Duke University Medical Center, Durham, NC, United States

Duke University School of Medicine

Introduction

Evidence is mounting that many patients who have recovered from acute COVID-19 have residual cardiopulmonary disease in the form of persistent, disabling symptoms characterized as **"long-haul COVID."** As the causes for dyspnea are multifactorial, there is an urgent need to not only elucidate potential cardiac and pulmonary causes, but also to monitor them longitudinally and non-invasively.

Hyperpolarized ^{129}Xe MRI and spectroscopy are sensitive to gas exchange abnormalities in a wide range of pulmonary/cardiopulmonary diseases, including interstitial lung diseases, COPD, asthma, pulmonary hypertension, and many others.

Here, we used dual MR imaging (cardiac MRI and hyperpolarized ^{129}Xe MRI) to characterize the impact of long-haul COVID-19 on cardiac and regional gas exchange function.

Methods

Patients with persistent and continued dyspnea at least 50 days after initial COVID-19 diagnosis (N=11) underwent hyperpolarized ^{129}Xe MRI and spectroscopy.

Subsets of subjects also underwent thoracic CT and cardiac MRI (including T1 and T2 relaxation times and late gadolinium enhancement). Subjects with *both* CT and cardiac MRI (N=3) are presented here as case studies.

Total	N = 11
Sex	6 M, 5F
Age	49 ± 13 yrs
Received cardiac MRI	5 (45%)
Received clinical CT	5 (45%)
Both CT and cMRI	3 (27%)

Table 1. *Study population.*

Presented here as Case Studies

^{129}Xe MRI Acquisition:

- Signals from gas phase (airspaces) and dissolved phase (interstitial barrier tissue uptake and red blood cell [RBC] transfer) were acquired during a single breath-hold[1].
- The gas-phase ^{129}Xe images were rendered into quantitative binning maps with thresholds derived from a healthy reference cohort, as described previously.[2]
- The ratio of RBC to membrane signal (RBC:M) was obtained from ^{129}Xe spectroscopy.[3]

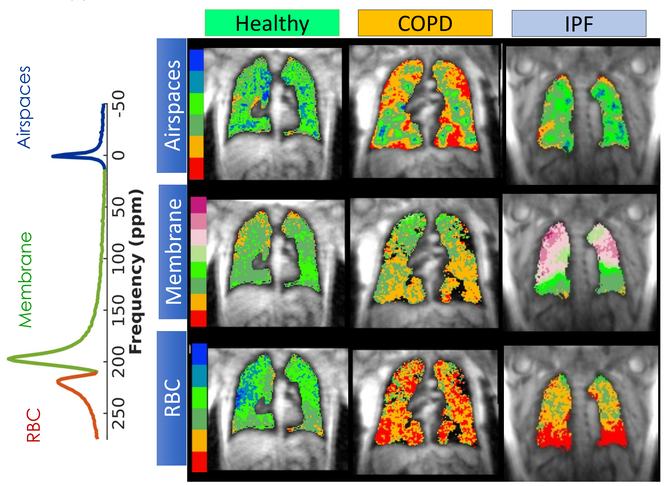
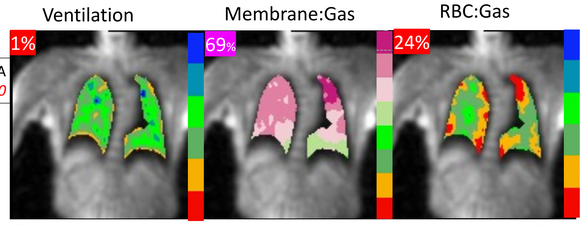


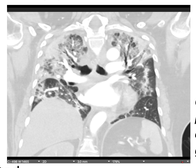
Figure 1. *Typical ^{129}Xe findings in a healthy subject, COPD, and IPF.*

Case Studies

Subject A



76 days post-dx. Striking increase in membrane signal with relatively preserved ventilation and RBC.



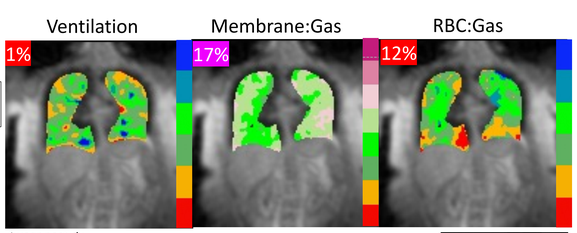
CT, 20 days post-DX: Upper peripheral consolidative opacities with central ground glass

Cardiac MRI, 43 days post-dx: Unremarkable.

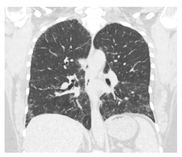
- 65F
- Unvaccinated
- Hospitalized one week after diagnosis with ARDS. Intubated. Discharged after 23 days.
- Severe SOB at imaging.

***Very high membrane signal* on ^{129}Xe MRI corresponding to regions of ground glass and consolidation on CT.** However, ventilation and RBC signals on ^{129}Xe are reasonably well preserved. Cardiac MRI unremarkable.

Subject B



1 year post-dx.



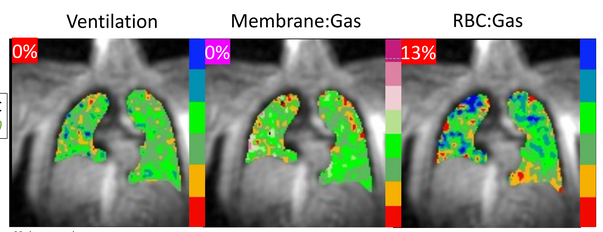
CT, 14mo post-DX: Diffuse mild-moderate peripheral areas of reticulation intermixed with groundglass opacities

Cardiac MRI, 13mo post-dx: Unremarkable.

- 45F
- COVID dx occurred pre-vaccination. Never hospitalized for COVID.
- **SOB, headaches, fatigue; over a year since Covid dx**
- Concurrent resolving subacute hypersensitivity pneumonitis

Mild but elevated membrane signal on ^{129}Xe together with mild-moderate ground glass and reticulation on CT. Preserved ventilation and RBC. Cardiac MRI findings unremarkable.

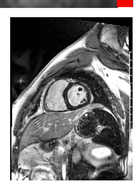
Subject C



82 days post-dx.

CT 26 days post-dx is unremarkable

Cardiac MRI, 113 days post-dx: Unremarkable.



- 36M firefighter
- Unvaccinated. Not hospitalized for COVID-19.
- **Profound fatigue and dyspnea, unable to perform most everyday activities. PFTs normal.**
- **Unremarkable CT, cardiac MRI, and ^{129}Xe findings suggest normal cardiopulmonary function**

Results

Table 2 (right) shows the overall pattern of gas exchange metrics in our full study population (N=11). Note that the pattern observed in our case studies is broadly consistent with that of the larger population: **widely varying membrane signal and RBC:M in the presence of preserved ventilation and limited RBC transfer impairment.**

Tabulated ^{129}Xe Results (N=11)

Metric	Median [Min - Max]
Ventilation Defect %	2 [0 – 9]%
High Membrane %	4 [0- 76]%
RBC Defect %	12 [4 - 24]%
RBC:Membrane	0.41 [0.13 – 0.70]

Table 2. *^{129}Xe metrics across study population. Note healthy RBC:M is approximately 0.59 ± 0.12)*

Discussion

We observed **a wide range of findings** on gas exchange ^{129}Xe MRI in this population of subjects with long-haul COVID-19. Some subjects exhibited **severely reduced measures of gas exchange** while others **had completely normal, healthy-looking imaging and spectroscopy**, despite the presence of persistent symptoms affecting quality of life.

Variability in RBC:M in our population appeared to be primarily driven by increased membrane signal, which ranged from normal (0% high membrane percent) to extremely high (76%).

- Ventilation was generally well-preserved
- RBC defects were present, but limited, with a maximum of 24% defect.
- Note that some degree of ventilation and RBC defects are expected with age (see abstract B28 #712)

Further, none of the subjects in our study who underwent cardiac MRI had abnormal cardiac structure/function findings.

In our three case studies, **Subject A** is an **archetype of an active, recently developed interstitial disease process: greatly elevated membrane signal in the presence of preserved ventilation and modestly impacted RBC,** with a severely decreased RBC:M as a result. CT findings of consolidation and ground glass opacity are consistent with this interpretation and appear to be spatially related to the increased membrane signal.

Subject B has a broadly similar, but much less extreme, pattern as Subject A. **Ventilation is pristine, membrane signal is modestly elevated, and RBC signal is largely intact.** CT findings indicate fibrotic lung disease, although this subject also has a concomitant diagnosis of hypersensitivity pneumonitis.

At the complete opposite end of the spectrum is **Subject C,** whose ^{129}Xe imaging and spectroscopy findings **appear completely healthy,** together with an unremarkable CT. Despite this overwhelming absence of any imaging findings and normal PFTs, **the subject has a severely impacted quality of life, including feeling like he is suffocating, brain fog, insomnia, and constant exhaustion. <u>The etiology of these symptoms is unknown.</u>**

Conclusion

^{129}Xe MRI is sensitive to gas exchange impairment in Long-Haul COVID-19 patients with normal cardiac structure and function.

- Variations in ^{129}Xe gas exchange appear to be driven largely by increased membrane signal
- Thus, high membrane % may be a "treatable trait" in long-haul COVID-19

Some subjects presented with normal clinical test results despite severe symptoms. In these "mystery" cases, **^{129}Xe MRI may be useful as a means of further determining the presence (or absence) of any subtle gas exchange abnormalities.**

Electronic Copy

References:

1. Niedbalski PJ et al. *Magn Reson Med* 2021.
2. Wang Z, et al. *Med Phys* 2017;44(6):2415–2428.
3. Bier EA et al. *NMR Biomed* 2019;32(1):e4029.

Acknowledgements:
Translating Duke Health Cardiovascular Disease Initiative Award