Multi-Site Harmonization of Hyperpolarized Xe-129 Gas-Exchange with 3D Single-Breath Chemical Shift Imaging: A Clinical Study with E-Cigarette Users

Jack B. Yang[1], Jaime Mata[1], John P. Mugler III[1], Bastiaan Driehuys[2], David Mummy[2], Jamie MacLeod[3], Yun Michael Shim[1,3]

[1]Radiology & Medical Imaging, University of Virginia, Charlottesville, VA, USA

[2]Radiology, Duke University, Durham, NC, USA

[3]Medicine, University of Virginia, Charlottesville, VA, USA

Financial Disclosure

- I do not have any relationships to report with ACCME defined ineligible companies.

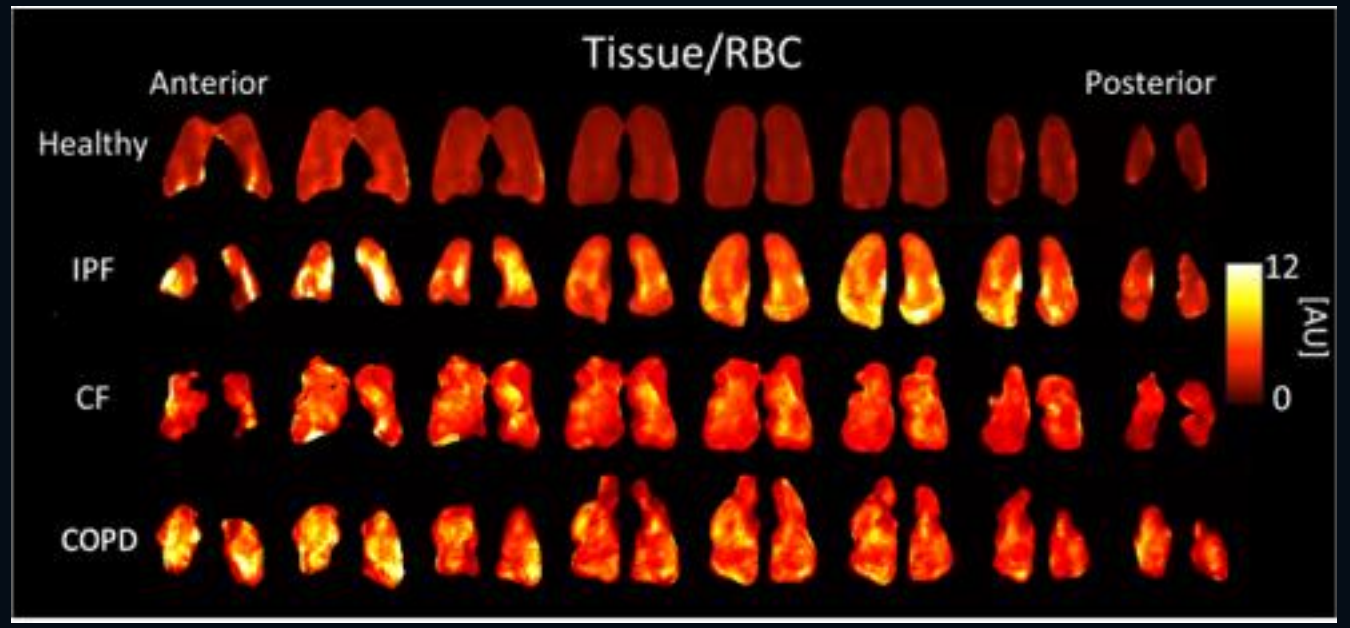
Background

- Electronic-cigarette (e-cigarette) use is classified by the Centers for Disease Control and Prevention as unsafe and is associated with outbreaks of severe lung injury [1].
- Besides nicotine, which is highly addictive, e-cigarettes contain numerous harmful unregulated substances such as reactive aldehydes and carbonyls, which frequently exceed federal occupational exposure levels [2].
- A detailed study on the effects of e-cigarette use is needed to understand its damaging effects on the pulmonary system.
- High-resolution CT is currently the gold-standard for the evaluation of interstitial lung diseases and provides high sensitivity for detecting subclinical interstitial abnormalities [3].
- However, even low-dose CT exposes participants to ionizing radiation and contributes to increased risk of cancer [4, 5].

Center for Disease Control (2024)
Ebersole et al. Tob Induc Dis.(2020)
Hatabu et al. The Lancet. Resp. Medicine (2020)
Sodickson et al. Radiology (2009)
Brenner et al. New England J. of Medicine (2007)

Background

- 3D Single-Breath Chemical Shift Imaging (3D SB-CSI) utilizes a combination of MR spectroscopy with hyperpolarized Xenon-129 (HP Xe-129) gas to generate 3D physiologic maps of the lung [6].
- Participants inhale a volume of hyperpolarized gas based on their forced vital capacity (FVC), which subsequently diffuses into the lung parenchyma (tissue) and red blood cells (RBCs).
- As a result, ventilation, tissue, and RBC maps can be quantified to locate areas of ventilation defects and abnormalities in gas diffusion.
- MR spectroscopic imaging and HP Xe-129 gas are both non-radioactive and have a low incidence rate of adverse effects [7,8].



Tissue/RBC maps generated through 3D Single-Breath Chemical Shift Imaging (3D SB-CSI) of healthy, idiopathic pulmonary fibrosis, cystic fibrosis, and COPD patients.

Guan et al. Tomography (2022)
Driehuys et al. Radiology (2012)
Shukla et al. Academic Radiology (2012)

Background and Rationale

- MRI using HP Xe-129 gas is an FDA-approved technology and has been shown to be able to discriminate between healthy lung tissue and diseased lung tissue, suggesting that it is a sensitive tool for detecting early-stage lung disease [9].

- Prior studies have not attempted harmonization of HP Xe-129 MRI methodologies between different institutions, which is necessary for future multi-site clinical trials.

- This study performed for the first time, repeatability studies of HP Xe-129 MR gas-exchange imaging of the same subjects at two different academic centers (Duke University and The University of Virginia).

Qing et al. Academic Radiology (2019).

Subject Cohorts

- Five healthy volunteers (three females and two males; 25.2±2.8 years) and two e-cigarette users (one female and one male; 19.5±0.5 years) underwent HP Xe-129 MRI studies at Duke University and The University of Virginia.

- Each healthy volunteer was rescanned within two months and each e-cigarette user within a month. E-cigarette users had used e-cigarettes on a regular basis (minimum of one pod per week) for at least 12 months.

- To facilitate harmonization, each technique was implemented by an investigator at one institution for the 3T MR scanners involved (Duke University: Siemens Prisma Fit, software Numaris/X VA30A; University of Virginia: Siemens Prisma Fit, software Numaris/4 VE11C).

- To maximize consistency, the same source-code base was used for the implementation at both sites, even though the software levels were different.

Procedure

- Subjects laid supine on the MR table and inhaled a volume of gas mixture equal to 20% of their FVC, with a total maximum volume capped at 1000 mL of isotopically enriched (83%) Xe-129 mixed with nitrogen.
- Xe-129 was polarized to ~25-30% using a commercial polarizer (Polarean, Durham, NC, USA).
- Subjects held their breath for less than 10s during the imaging sequence, during which proton (2D-GRE sequence with spiral trajectories; TA < 2 s) or ventilation images (TA ~2.7 s) were acquired.
- Ventilation and gas-exchange imaging post-processing, using the binning method, was performed at Duke University. Secondary statistical analyses were done at the University of Virginia, using paired t-test for the comparisons.

Results – Figure 1

- Figure 1 demonstrates ventilation levels detected for the same subject (Subject #03 - Healthy) that was imaged at both institutions.
- When spectroscopic maps were generated, similar values and images were identified at both sites for detailed global analyses.
- Please note that the measured TCV was higher at Site #1 (Duke – 3.85L) than at Site #2 (UVA – 3.45L)

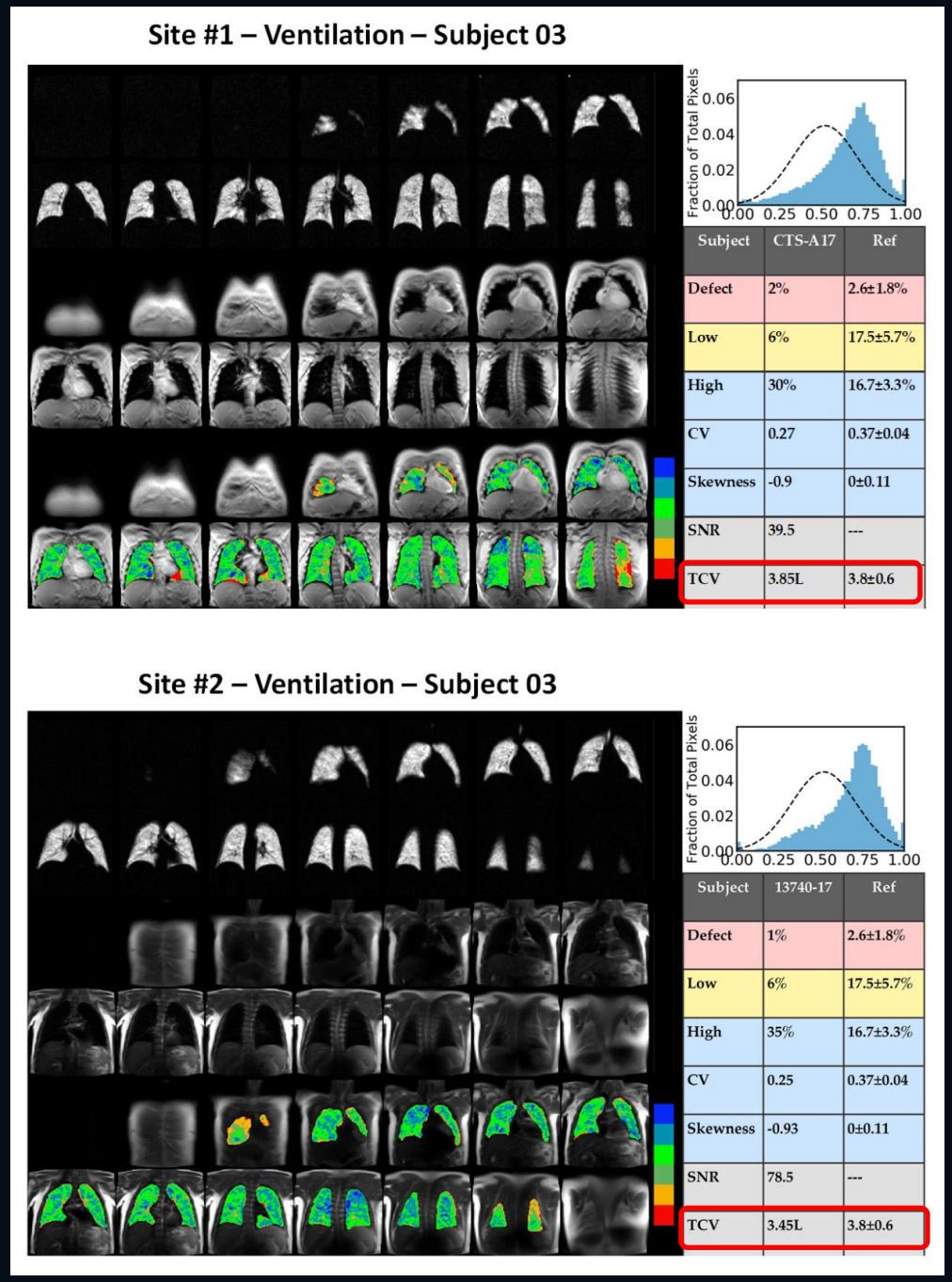


FIGURE 1 - Two top rows of matrix, show lung ventilation images from the 2D-GRE; two middle rows show proton MRI; two bottom rows show the color code ventilation maps superimposed on the proton MRI (red = ventilation defect (no ventilation); orange = low ventilation; green = normal ventilation; blue = higher than normal ventilation). On the right side is the respective numerical analysis and pixel histogram. SNR = Ventilation image signal-to-noise ratio. TCV = Total lung capacity volume in Liters.

Results – Figure 2

- Figure 2 demonstrates gas-exchange results for a single subject (Subject #3 - Healthy), which are broken down into ventilation, barrier, and RBC categories respectively.
- Please note the similar values that were found within each category, as well as similar spectroscopic histograms.
- Please note that the measured inflation is higher at Site#1 (Duke – 4.67 L) than site#2 (UVA – 3.3L)

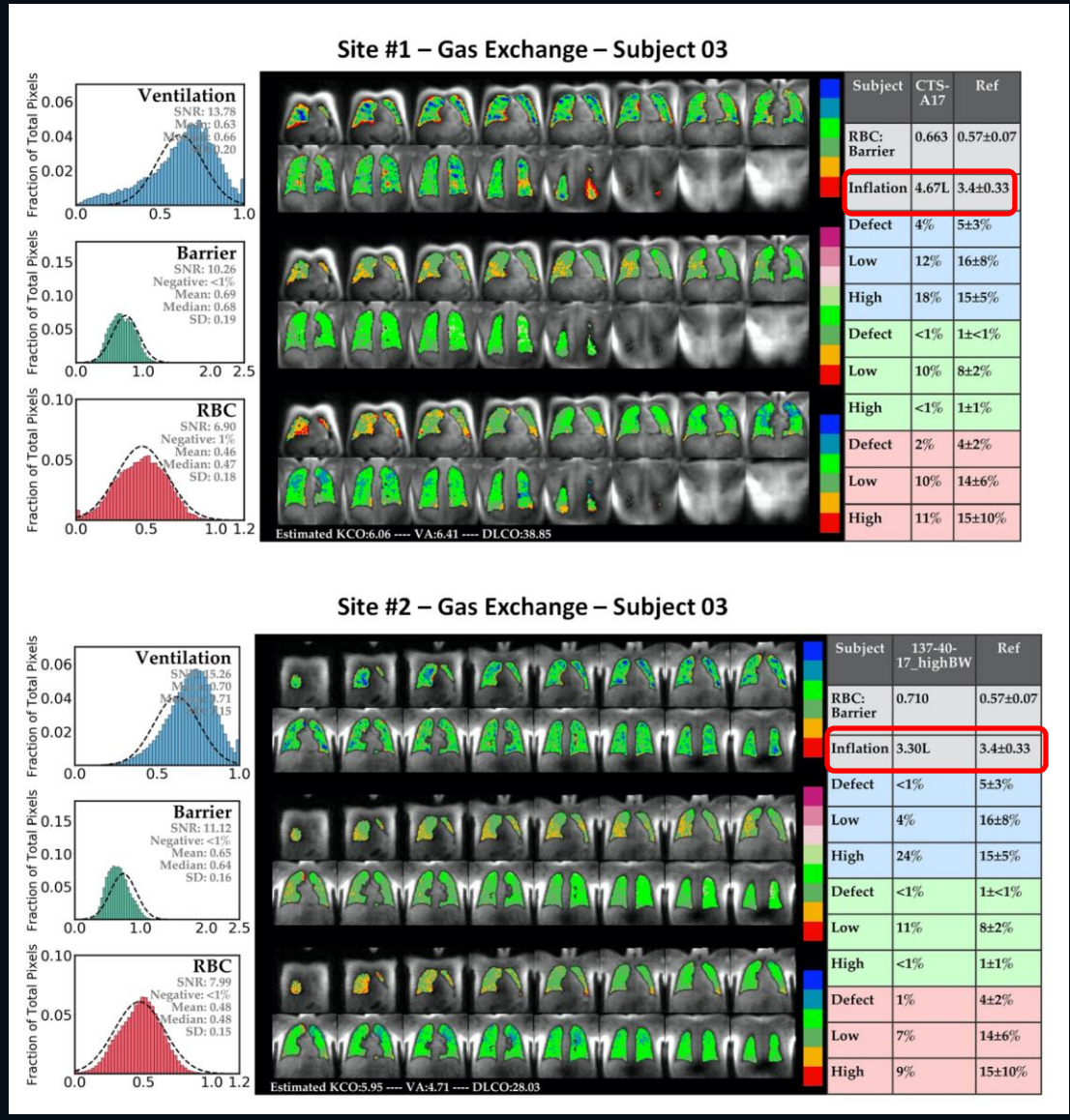


FIGURE 2 – Two top rows of the central imaging matrix, show Xe-129 MRI lung ventilation (color code identical to ventilation maps on Figure 1). Two middle rows show Xe-129 distribution in the lung membrane. Two bottom rows show maps from Xe-129 distribution in the RBC. Histograms are from the pixel distribution of the respective maps on their right side. Numerical analyses are from the lung maps at the center (blue for the ventilation; green for the membrane=barrier; pink for the RBC) and reflect the percentage of pixels with no existence in a certain area (defect), with low values (low) and with higher than the normal values (high).

Results – Global-Analysis Metrics

- Figure 3 demonstrates quantitative differences between global-analysis metrics for each subject.
- Please note the statistically insignificant differences for each subject for ventilation and gas exchange values (membrane/RBC's)
- Signal-to-noise ratio for the ventilation scans was the only statistically significant parameter (p=0.027) to differ between the sites.
- There was good correlation between the two sites for RBC/Tissue values, with consistent bias of gas exchange parameters with Duke having consistently slightly higher values than those from UVA

		Differences between sites														
		Ventilation					Gas Exchange - Membrane				Gas Exchange - RBC					
		Defect [%]	Low [%]	Normal [%]	High [%]	SNR	Mean	Median	SD	SNR	Mean	Median	SD	SNR	RBC:Barrier	Inflation [L]
Subject 01	healthy	0	-3	7	-4	-5.32	0.25	0.27	0.04	6.34	0.26	0.29	0.01	5.44	0.123	-0.42
Subject 02	healthy	2	0	-7	5	-2.35	-0.32	-0.33	-0.05	-6.58	-0.24	-0.27	-0.05	-4.47	-0.139	0.44
Subject 03	healthy	1	0	4	-5	-1.48	0.04	0.04	0.03	-0.86	-0.02	-0.01	0.03	-1.09	-0.047	1.37
Subject 04	healthy	-1	-4	14	-9	-26.86	-0.34	-0.36	-0.01	-37.78	-0.08	-0.1	0.08	-10.91	-0.005	0.07
Subject 05	healthy	0	-3	13	-10	-7.4	-0.44	-0.44	-0.13	-9.91	-0.32	-0.36	-0.07	-7.34	0.01	0.3
Subject 06	e-cig	-3	-9	-8	20	-9.97	-0.26	-0.27	-0.03	-15.81	-0.27	-0.3	-0.07	-13.35	-0.073	0.45
Subject 07	e-cig	5	4	-14	5	-13.89	0.01	0.01	0.06	-11.82	0.05	0.05	0.03	-3.03	0.096	-0.28
	mean	0.57	-2.14	1.29	0.29	-9.61	-0.15	-0.15	-0.01	-10.92	-0.09	-0.10	-0.01	-4.96	-0.01	0.28
	median	0.00	-3.00	4.00	-4.00	-7.40	-0.26	-0.27	-0.01	-9.91	-0.08	-0.10	0.01	-4.47	-0.01	0.30
	SD	2.321	3.758	10.194	9.794	8.090	0.234	0.243	0.060	12.902	0.191	0.214	0.054	5.838	0.085	0.546
	p-value	0.569	0.212	0.768	0.945	0.027	0.164	0.171	0.619	0.084	0.299	0.295	0.804	0.082	0.891	0.263

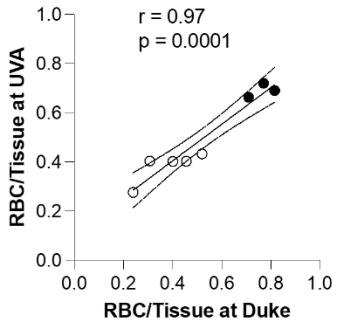


FIGURE 3 - Table shows the quantitative differences between global-analysis metrics from each site for each subject (value from Duke University subtracted from value from University of Virginia). Plot (Below) shows good correlation between the two sites for the RBC/Tissue. Open circles belong to healthy subjects and dark circles to e-cig users.

Discussion

- Harmonization of HP Xe-129 MRI gas-exchange and ventilation imaging methodology among the two sites was successfully achieved, opening the way for a large clinical trial with these two institutions.

- Among both healthy and e-cigarette users, ventilation and gas exchange values were similar for each subject at both institutions.

- Consistent bias of gas exchange parameters were noted, with Duke university having values that were higher than that of UVA. This may be due to lung-inflation levels; for 5 out of 7 subjects, the lung inflation level was higher at Duke than at UVA.

- Signal to Noise ratio for ventilation was the only measurement noted to be different between the two institutions. This may be related to lung-inflation level as well, or with slight differences in polarization of the Xe-129 gas.

Strengths/Limitations

Strengths:

- This is the first study to assess harmonization of Xe-129 MRI gas-exchange and ventilation imaging methodology across two different academic institutions.

- Participants in both a healthy control and disease cohort were shown to have good harmonization with no significant differences in calculated values, except for ventilation signal to noise ratio.

Limitations:

- Patients in both cohorts were young, with an average of ~25 in the healthy cohort and ~20 years old in the e-cigarette cohort.

- For this study, specific disease progression was not tracked, and it is unknown how significant lung damage would affect the distribution patterns created and effects on harmonization

Summary

- In this experiment, we demonstrate successful harmonization of HP Xe-129 MRI imaging methodology across two different academic institutions.
- Global-analysis values were found to have no significant differences when compared between the two institutions for the same participants.
- This paves the way for developing future experiments with HP Xe-129 MRI imaging for the use of studying various disease pathologies, and demonstrates the repeatability of HP Xe-129 MR imaging at different institutions with the same clinical patients.

Thank You!

Contact Information: Jrv4sg@uvahealth.org

References

1. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/Quick-Facts-on-the-Risks-of-E-cigarettes-for-Kids-Teens-and-Young-Adults.html
2. Ebersole, Jeffrey, Vera Samburova, Yeongkwon Son, David Cappelli, Christina Demopoulos, Antonina Capurro, Andres Pinto et al. "Harmful chemicals emitted from electronic cigarettes and potential deleterious effects in the oral cavity." Tobacco induced diseases 18 (2020).
3. Hatabu, Hiroto, Gary M. Hunninghake, Luca Richeldi, Kevin K. Brown, Athol U. Wells, Martine Remy-Jardin, Johny Verschakelen, et al. “Interstitial Lung Abnormalities Detected Incidentally on CT: A Position Paper from the Fleischner Society.” The Lancet. Respiratory Medicine 8, no. 7 (July 2020): 726–37. https://doi.org/10.1016/S2213-2600(20)30168-5.
4. Sodickson, Aaron, Pieter F. Baeyens, Katherine P. Andriole, Luciano M. Prevedello, Richard D. Nawfel, Richard Hanson, and Ramin Khorasani. “Recurrent CT, Cumulative Radiation Exposure, and Associated Radiation-Induced Cancer Risks from CT of Adults.” Radiology 251, no. 1 (April 2009): 175–84. https://doi.org/10.1148/radiol.2511081296.
5. Brenner, David J., and Eric J. Hall. “Computed Tomography — An Increasing Source of Radiation Exposure.” New England Journal of Medicine 357, no. 22 (November 29, 2007): 2277–84. https://doi.org/10.1056/NEJMra072149.
6. Guan, Steven, et al. "3D Single-Breath Chemical Shift Imaging Hyperpolarized Xe-129 MRI of Healthy, CF, IPF, and COPD Subjects." Tomography 8.5 (2022): 2574-2587.
7. Driehuys, Bastiaan, Santiago Martinez-Jimenez, Zackary I. Cleveland, Gregory M. Metz, Denise M. Beaver, John C. Nouls, S. Sivaram Kaushik, et al. “Chronic Obstructive Pulmonary Disease: Safety and Tolerability of Hyperpolarized 129Xe MR Imaging in Healthy Volunteers and Patients.” Radiology 262, no. 1 (January 2012): 279–89. https://doi.org/10.1148/radiol.11102172.
8. Shukla, Yajur, Andrew Wheatley, Miranda Kirby, Sarah Svenningsen, Adam Farag, Giles E. Santyr, Nigel A. M. Paterson, David G. McCormack, and Grace Parraga. “Hyperpolarized 129Xe Magnetic Resonance Imaging: Tolerability in Healthy
9. Qing K, Tustison NJ, Mugler JP III, et al. Probing changes in lung physiology in COPD using CT, perfusion MRI, and hyperpolarized Xenon-129 MRI. Acad Radiol 2019; 26:32634.