Online Methods:

Human Subjects

Thirty-four COPD and eleven healthy subjects were included in the study. All subjects were recruited at the University of Virginia under Institutional Research Board (IRB) approval and enrolled after informed consent to participate was obtained. COPD was defined by post-bronchodilator (BD) Forced Expiratory Volume in 1 second/Forced Vital Capacity ratio (FEV_1/FVC) <0.7. The bronchodilator used was 2.5 mg albuterol sulfate given via a nebulizer to ensure the most optimal delivery of BD. All underwent complete PFT which included pre- and post-BD spirometry, lung volumes, DLCO, six-minute walk distance (6MWD), MDCT, and HXeMRI.

Image Acquisition. Processing, and Analysis

Computed Tomography

MDCT was performed based on the COPDGene protocol[6]. Subjects were coached to breathe to maximal inhalation and hold their breath for the CT scan. CT was acquired using a SOMATOM Definition Flash (Siemens Healthcare, Forchheim, Germany) at 120 KV, and 200 mAs. The in-plane spatial resolution was approximately 1 x 1 mm with slice thickness of 0.75 mm. CT images of the lungs were segmented using an automated method as previously described [8 9]. Voxels with Hounsfield unit values <-950 were presented as a percentage of total lung volume, defining the emphysema biometric $\%LAA_{-950}$. Pulmonary artery (PA) diameter to aorta diameter ratios were measured on axial images at the level of the PA bifurcation by a trained chest radiologist and 2 additional blinded readers trained in the technique. The presented values reflect the mean of these 3 readings.

MRI and Hyperpolarized Xenon Image Acquisition

Combined Hyperpolarized Xenon-129 and conventional proton MR imaging were acquired during a single breath hold using a 1.5T commercial whole-body MR scanner (Avanto; Siemens Medical Solutions, Malvern PA). Hyperpolarized Xe-129 MRI has been well described as a modality for functional pulmonary imaging, allowing for quantifiable, functional characterization of both ventilation and gas transfer. Due to distinct MR spectral peaks ascertainable with dissolved-phase imaging, xenon content in 3 mutually exclusive microcompartments can be quantified, namely airspace (gas), interstitium/parenchyma (barrier) and red blood cells (RBCs). Hyperpolarized Xe-129 MR images were acquired at spatial resolution of 7.6 x 7.6 x 17 mm^3 over an acquisition time of approximately 10 seconds. A 3D proton pulse sequence was appended to the dissolved-phase acquisition with an acquisition time of 3 seconds, an acceleration factor of three and an isotropic resolution of approximately 4 mm resulting in a total acquisition time of less than 15 seconds. A flexible, circularly-polarized, vest-shaped chest RF coil (Clinical MR Solutions, Brookfield, Wisconsin) was used for all hyperpolarized Xe-129 MRI acquisitions. Proton MRI acquisitions employed the scanner's conventional body RF coil. Enriched xenon gas (87% Xe-129) was polarized using a Polarean 9820 system (Polarean, Durham, North Carolina) with achieved polarization of 25-40%. Subjects exhaled to residual volume, and then inhaled a gas mixture (Xe-129 +N_2 gas) to a resting volume equivalent to one-third of their forced vital capacity (based on spirometry) and then held their breath for the duration of the HP Xe-129 MRI acquisition. Four unique image sets were re-constructed from the single breath-hold Xenon-129/Proton acquisition as follows: (1) Proton images of the lungs characterizing anatomy; (2) Xenon-129 "gas" images characterizing ventilation; (3) Xenon-129 "tissue" images characterizing gas uptake by lung interstitium; and (4) Xenon-129 "RBC" images characterizing gas uptake by the circulating red blood cells (RBCs). Ventilation-based segmentation was performed for each of the Xenon-129 images. defect was categorized into: (1) non-ventilating [VDP]; (2) hypoventilating; (3) ventilating; and (4) hyperventilating. We note that both ^{129}Xe ventilation MRI and dissolved phase MRI yield ^{129}Xe "gas" images. For most of the subjects, ^{129}Xe ventilation MRI was used to quantify gas flow limitations. However, in subjects who

did not undergo ^{129}Xe ventilation MRI, dissolved phase MRI derived ventilation scans were used for gas flow quantification. Two ratio maps were generated for all subjects: (1) xenon content in interstitium normalized to alveolar content [T/G] and (2) red blood cell content normalized to alveolar content [R/G] in (Figure 1). Accelerated proton images of the lung were reconstructed using compressed sensing as described previously. Lungs were segmented and subsequently applied as masks to the Xe-129 reconstructions to quantify gas uptake in each subject. Image registration and segmentation were processed using Advanced Normalization Tools package [ANTs website, http://picsl.upenn.edu/software/ants/].

Statistics:

All data analysis and visualization were performed using the Prism Graphpad Software Package version 8.2.1. Continuous variables in greater than 2 group comparisons were analyzed using the non-parametric Kruskal-Wallis statistical test on ranks. Dunn's test for multiple comparisons of selected groups was used to analyze the significance of between group comparisons. A p value of less than 0.05 was considered statistically significant. P values in multivariable correlation analysis were adjusted for multiple testing.

Online Table 1. Characteristics of the Study Groups

	Healthy (n = 11)	COPD (n = 34)	p value
Age average, median [IQR]	56.0 [48.0,69.0]	62.0 [57.5,69.0]	0.106*
Sex, male, n (%)	5 (45%)	18 (53%)	0.738**
BMI, median [IQR]	23.0 [21.0,28.6]	25.3 [22.7, 27.8]	0.649*
Current Smokers, n (%)	0	14 (41%)	n/a
Pack Years, median [IQR]	0	40.0 [29.0, 62.2]	<0.001*
PRN inhaler only, n (%)	n/a	5 (15%)	n/a
Inhaled or Systemic ICS, n (%)	n/a	15 (44%)	n/a
LAMA, n (%)	n/a	21 (62%)	n/a
LABA, n (%)	n/a	13 (38%)	n/a
FEV_1/FVC, median [IQR]	0.74 [0.73,0.76]	0.56 [0.44,0.62]	<0.001*
%FEV_1 predicted, median [IQR]	101 [98,109]	62.5 [42,79]	<0.001*
%RV predicted, median [IQR]	96 [84,106]	147 [114,179]	<0.001*
%DLCO predicted, median [IQR]	85 [82,94]	57 [48,69]	<0.001*
% LAA_{-950}, median [IQR]	0.008 [0.005,0.314]	3.18 [1.31,12.6]	<0.001*

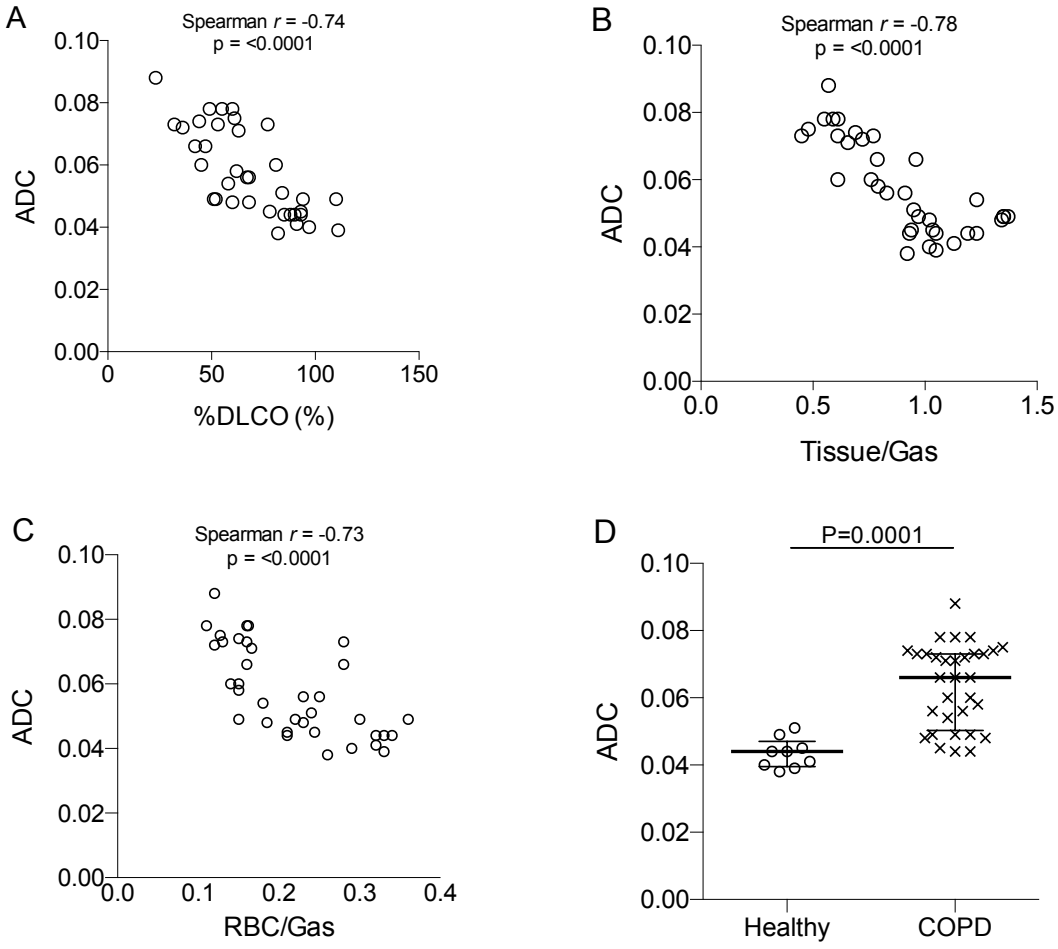
Notes: IQR = interquartile range. BMI = body mass index. PRN = as needed. ICS = inhaled corticosteroid. LAMA = long acting muscarinic antagonist. LABA = long acting β-agonist. FEV_1 = Forced Expiratory Volume in 1 second. FVC = Forced Vital Capacity. %FEV_1 = Percent predicted FEV_1. %RV = Percent Predicted Residual Volume. %DLCO = percent predicted value of carbon monoxide diffusion capacity. %LAA_{-950} = percent of the lung with emphysematous changes detectable by MDCT. P values denoted with * were generated by Mann-Whitney Test. P values denoted with ** were generated by Fisher's Exact test.

Online Table 2: Subtype-demographics comparisons.

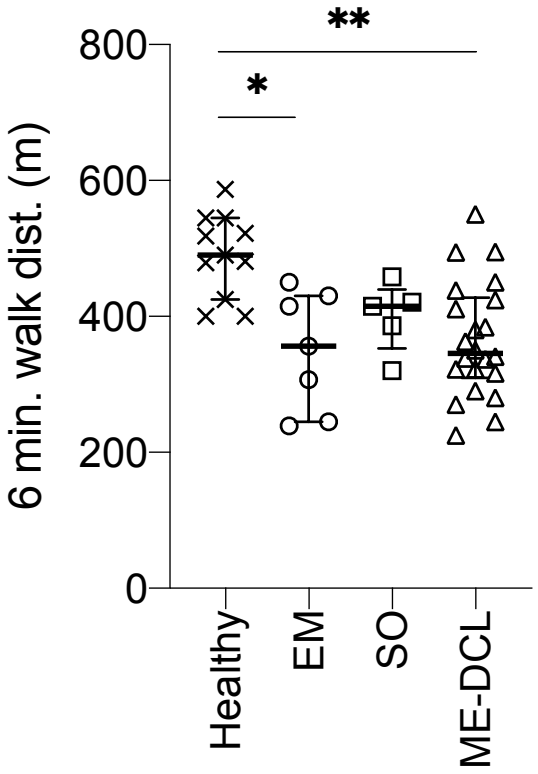
	Emphysema (n = 7)	**SO (n = 5)**	**ME-DCL (n = 22)**	**Healthy (n = 11)**	**p value**
Age average, median [IQR]	74.0 [56.0,80.0]	60.0 [55.0,79.5]	62.0 [58.0,67.3]	56.0 [48.0,69.0]	0.326
Male Sex, n (%)	6 (86%)	3 (60%)	9 (39%)	5 (42%)	n/a
BMI, median [IQR]	24.1 [22.0,26.5]	30.0 [26.6,30.6]	24.5 [20.5,27.5]	23.0 [21.01,28.6]	0.098
Current Smokers, n (%)	1 (14%)	1 (20%)	12 (55%)	0	n/a
Pack Years, median [IQR]	30.0 [23.0,50.0][a]	30 [21,39][a]	50.0 [32.5,80.0][a]	0[b]	<0.001
PRN inhaler only, n (%)	1 (14%)	1 (20%)	3 (14%)	n/a	n/a
Inhaled or Systemic ICS, n (%)	3 (43%)	1 (20%)	11 (50%)	n/a	n/a
LAMA, n (%)	5 (71%)	1 (20%)	15 (68%)	n/a	n/a
LABA, n (%)	2 (29%)	0	11 (50%)	n/a	n/a
FEV_1/FVC, median [IQR]	0.41 [0.35,0.45][a]	0.64 [0.57,0.67][b]	0.58 [0.47,0.62][b]	0.74 [0.73,0.76][c]	<0.001
%FEV_1 predicted, median [IQR]	38 [35,49][a]	76 [69,85][b]	64 [46,81][b]	101 [98,109][c]	<0.001
%RV predicted, median [IQR]	175 [144,190][a]	149 [125,210][a]	131 [106,178][a]	96 [84,106][b]	<0.001
%DLCO predicted, median [IQR]	53 [45,60][a]	93 [85,102][b]	53 [46,67][a]	85 [82,94][b]	<0.001
% LAA_{-950}, median [IQR]	30.2 [17.7,41.4][a]	1.1 [0.3,3.8][b]	3.1 [1.3,10.7][b]	0.008 [0.005,0.314][c]	<0.001

Notes: IQR = interquartile range. BMI = body mass index. PRN = as needed. ICS = corticosteroid. LAMA = long acting muscarinic antagonist. LABA = long acting β-agonist. FEV_1 = Forced Expiratory Volume in 1 second. FVC = Forced Vital Capacity. %FEV_1 = Percent predicted FEV_1. %RV = Percent Predicted Residual Volume. %DLCO = percent predicted value of carbon monoxide diffusion capacity. %LAA_{-950} = percent of the lung with emphysematous changes detectable by MDCT. All p values were generated by Kruskal-Wallis test. Different superscripts accompanying the 95% confidence intervals denote statistically different groups at the $p<0.05$ significance level, while the same superscript denotes no significant difference at the $p<0.05$ significance level.

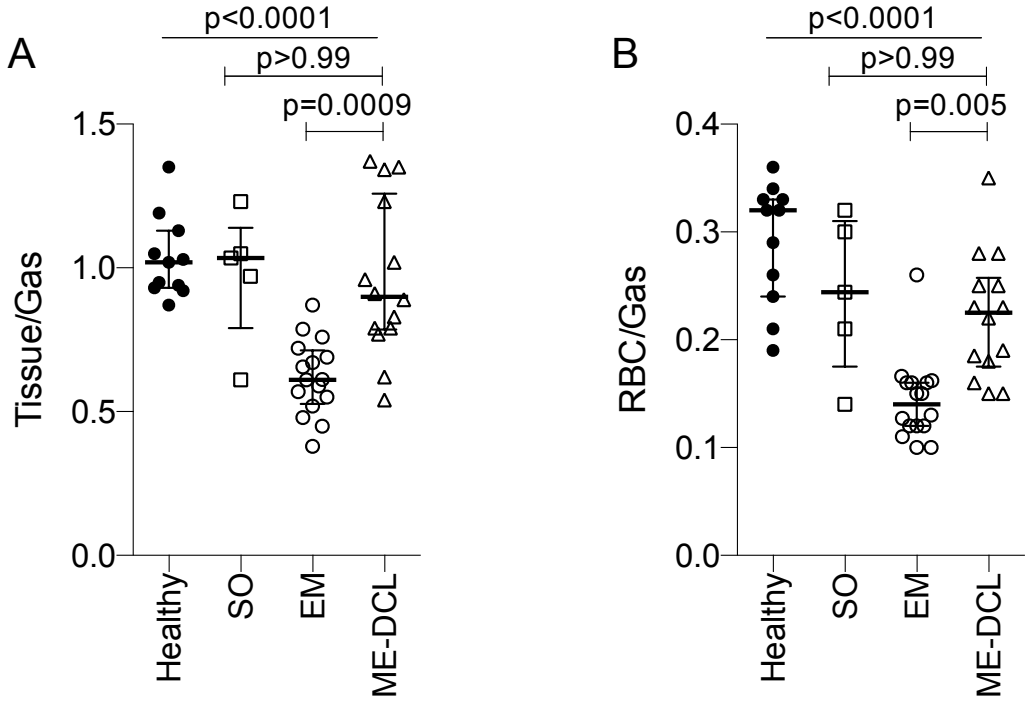
Online Figure 1. (A) Correlation of HXeMRI Apparent Diffusion Coefficient (ADC) with DLCO% (Spearman *r*=-0.74), (B) Correlation of HXeMRI ADC with T/G (*r*=-0.78), (C) Correlation of HXeMRI ADC with R/G (*r*=-0.73), and (D) Comparison between healthy and COPD subjects' ADC reported for a limited number of study subjects (n = 38 of 45) for whom ADC data was available.



Online Figure 2. Six-minute walk distance (6MWD) in meters at rest in healthy (x), EM (○), SO (□), and ME-DCL (△) groups. Kruskal-Wallis analysis was significant ($p<0.05$). * denotes $p<0.05$ and ** denotes $p<0.01$ in Dunn's multiple comparisons analysis.



Online Figure 3. Alternative categorization of COPD subjects into three mutually exclusive phenotypes by applying binary %DLCO and $\%LAA_{-950}$ thresholds: Subjects with $\%LAA_{-950} \geqq 6.8\%$ and $\%DLCO \leqq 80\%$ were designated "emphysema-predominant" (EM, n=16, "o")[9]. Subjects with $\%LAA_{-950} < 6.8\%$ and $\%DLCO \geqq 80\%$ were designated "simple obstruction" (SO) (n=5, "□"), while subjects with $\%LAA_{-950} < 6.8\%$ and $\%DLCO < 80\%$ were designated "ME-DCL" (n=14, "△"). (A) Tissue-to-gas ratio in healthy (x), SO (□), EM (○), and ME-DCL (△) groups. (B) RBC-to-gas ratio in healthy (x), SO (□), EM (○) and ME-DCL (△) groups. Kruskall Wallis analysis was performed for multi-group comparison and Dunn's multiple comparisons between ME-DCL and EM or ME-DCL and SO.



Online Figure 4. (A) Percent of the lung with reduced ventilation comparison between healthy and COPD subjects ($p<0.0001$). Mann-Whitney Test was performed for data. (B) Percent of the lung with reduced ventilation comparison COPD phenotypes defined by percent predicted value of carbon monoxide diffusion capacity (%DLCO) and percent of the lung with emphysematous changes detectable by MDCT ($\%LAA_{-950}$). Healthy (x), EM (○), SO (□), and ME-DCL (△) groups. Kruskall Wallis analysis was performed for multi-group comparison and Dunn's multiple comparisons between ME-DCL and EM or ME-DCL and SO.