Supplementary Material

Supplementary Data 1: Lung volume measurement optimization

To obtain accurate lung volume, the breathing strategy was optimized with five naive rats. Lung volume calculation was mainly affected by the residual paramagnetic oxygen, which would accelerate hyperpolarized xenon signal decay and reduce the longitudinal relaxation time of hyperpolarized xenon. Hence, the relationship of measured lung volume and xenon flushing times was evaluated. With the flushing times increased, the larger lung volume would be obtained. The measured lung volume will be stable when the flushing times is more than 2, as shown in supplementary Fig. S1. The flushing times of 3 was chosen for lung volume measure. For xenon flushing, the tidal volume is 3 mL, and the other acquisition parameters were the same as described in the section 2.3.

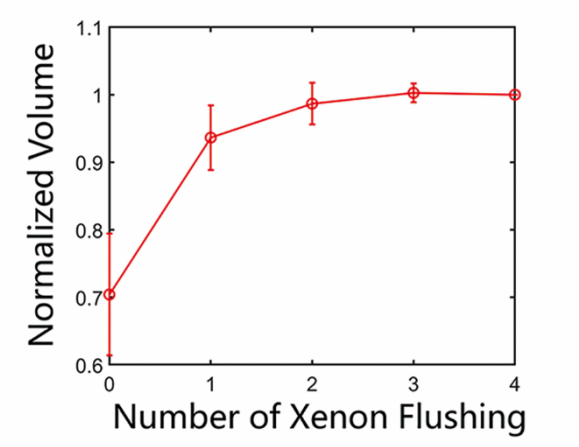

Fig. S1. The relationship of measured lung volume with xenon flushing. Each datapoint was normalized by the max volume, and each data was the average of five rats, shown as mean ± standard deviation.

Supplementary Data 2: Global and regional lung compliance calculation by CT

The lung parenchyma was obtained by segmenting CT images using Hounsfield Unit (HU) thresholding. Global static lung compliance measured with CT (C_{CT}) was calculated by linearly fitting using the following equation:

$$\Delta V_{CT}(i) = C_{CT} \cdot \Delta P_{CT}(i), \text{ i} = 1, \ldots, \text{n} \quad (1)$$

$$\Delta V_{CT}(i) = V_{CT}(i) - V_{CT}(0);\ \Delta P_{CT}(i) = P_{CT}(i) - P_{CT}(0)$$

Where $V_{CT}(i)$ and $V_{CT}(0)$ are the total lung volume measured using the CT lung images under the airway pressure $P_{CT}(i)$ and $P_{CT}(0)$, i = 1…n, respectively; n represents the number of pressure points.

For the calculation of 3D regional lung compliance measured with CT (C_{CT_map}), segmented CT lung images acquired under different airway pressures of $P_{CT}(1)$, …, $P_{CT}(n)$ were registered to the image with minimal pressure ($P_{CT}(0)$). Then, the Jacobian determinant maps $J(\Psi_{CT\text{-}P(i)})$ were calculated from the deformation field $\Psi_{CT\text{-}P(i)}$, i=1…n, and volume maps were calculated as follows:

$$\text{Vol}(P_{CT}(i), x) = J(\Psi_{CT\text{-}P(i)}, x) \bullet \text{Vol}(P_{CT}(0), x), \text{ i} = 1, \ldots, \text{n} \quad (2)$$

where $\text{Vol}(P_{CT}(i), x)$ and $J(\Psi_{CT\text{-}P(i)}, x)$ are the voxel volume and Jacobian determinant at position x in the CT images under pressure $P_{CT}(i)$, respectively. The C_{CT_map} was calculated by linearly fitting using the following equation:

$$\Delta Vol_{CT}(i,x) = C_{CT\_map}(x) \cdot \Delta P_{CT}(i), \text{ i} = 1, \ldots, \text{n} \quad (3)$$

$$\Delta Vol_{CT}(i,x) = Vol(P_{CT}(i), x) - Vol(P_{CT}(0), x);\ \Delta P_{CT}(i) = P_{CT}(i) - P_{CT}(0)$$

where $C_{CT\_map}(x)$ represents the lung compliance at position x in the CT image at pressure $P_{CT}(0)$.

Supplementary Data 3: Repeatability of C_{Xe} and C_{Xe_map} measurement

To evaluate the repeatability of C_{Xe} and C_{Xe_map} measurement, ^{129}Xe ventilation MRI was repeated in four naive rats for three times. The acquisition parameters and breath strategies were the same with that described in the section 2.3 of the manuscript. The measured C_{Xe} and C_{Xe_map} are summarized in Table S1, and the measured mean coefficient of variation of both parameters was less than 5 %, indicating a good repeatability.

Table S1

Repeated measurement of C_{Xe} and C_{Xe_map}.

	Rat 1	Rat 2	Rat 3	Rat 4
C_{Xe} (mL/H_2O)				
1	0.39	0.46	0.33	0.31
2	0.39	0.45	0.37	0.31
3	0.36	0.45	0.39	0.33
Mean ± SD	0.38 ± 0.02	0.45 ± 0.01	0.36 ± 0.03	0.32 ± 0.01
CV	5.3 %	2.2 %	8.3 %	3.1 %
Mean CV	4.7 %			
C_{Xe_map} (10^{-4}mL/H_2O) *				
1	0.47 ± 0.02	0.50 ± 0.02	0.41 ± 0.02	0.34 ± 0.02
2	0.47 ± 0.02	0.51 ± 0.02	0.43 ± 0.01	0.36 ± 0.02
3	0.45 ± 0.02	0.50 ± 0.02	0.46 ± 0.02	0.37 ± 0.02
Mean ± SD	0.46 ± 0.01	0.50 ± 0.00	0.43 ± 0.02	0.36 ± 0.01

CV	2.2 %	1.0 %	4.7 %	2.8 %
Mean CV	2.7 %			

* C_{Xe_map} is presented as the means ± SD for the whole lung of each rat.

Fig. S2 shows the C_{Xe_map} and goodness-of-fit (R^2) maps from a representative rat. The distribution of C_{Xe_map} was similar in three measurements.

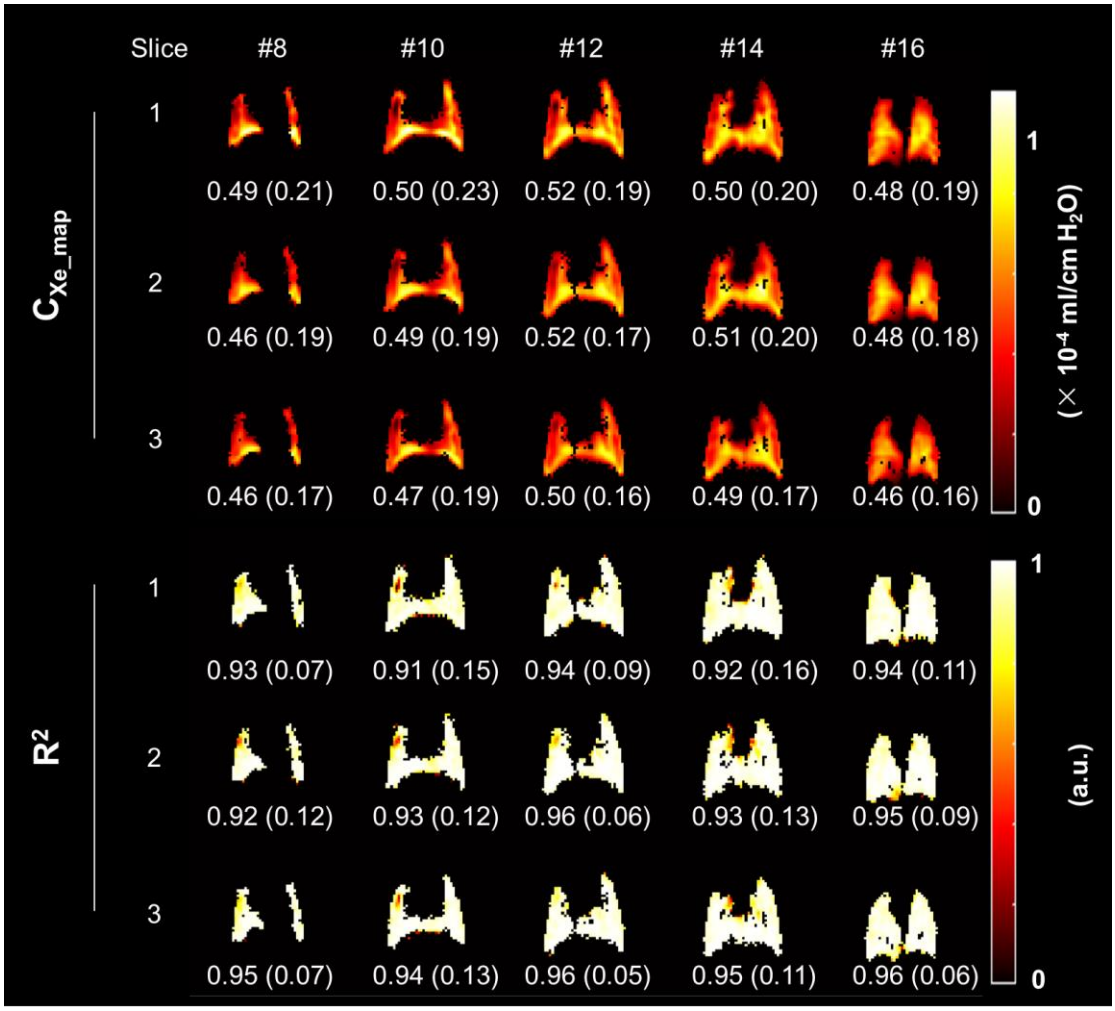

Fig. S2. C_{Xe_map} and goodness-of-fit (R^2) maps from a typical rat. Similar results were found in the three measurements, and the values below each image were the mean ± standard deviation.

Supplementary Data 4: Test of normality of data in the manuscript

Table S2

Test of normality of data in manuscript.

		Test of normality					
		Control			Fibrosis		
Method	Parameters	S-W test statistic	df	p-value	S-W test statistic	df	p-value
PFTs	IC	0.929	10	0.441	0.934	10	0.486
	FVC	0.987	10	0.991	0.944	10	0.599
	FEV_{100}	0.950	10	0.673	0.978	10	0.954
	TLC	0.916	10	0.327	0.918	10	0.344
	C_{qs}	0.899	10	0.213	0.902	10	0.228
MRI	C_{Xe}	0.943	10	0.588	0.947	10	0.632
	C_{Xe_map}	0.962	10	0.804	0.875	10	0.114
	C_{Xe_map} in apical[#]	**0.779**	**10**	***0.008***	0.963	10	0.822
	C_{Xe_map} in basal	0.964	10	0.834	0.959	10	0.774
	C_{Xe_map} in anterior	0.956	10	0.735	0.967	10	0.857
	C_{Xe_map} in posterior[#]	**0.782**	**10**	***0.009***	0.914	10	0.312
	C_{Xe_map} in right	0.918	10	0.344	0.951	10	0.682
	C_{Xe_map} in left	0.865	10	0.088	0.944	10	0.599
	R_{A-B}	0.909	10	0.273	0.907	10	0.262
	R_{A-P}	0.922	10	0.377	0.888	10	0.161
	R_{R-L}[#]	**0.794**	**10**	***0.012***	0.947	10	0.638
	R^2 for P-V fitting[#]	**0.839**	**10**	***0.043***	0.899	10	0.211
	Kurtosis	0.940	10	0.555	0.875	10	0.113
	Skewness	0.945	10	0.575	0.942	10	0.576
CT	C_{CT}	0.957	9	0.765	0.873	10	0.191
	C_{CT_map}	0.936	9	0.538	0.895	10	0.107
	C_{CT_map} in apical	0.898	9	0.242	0.951	10	0.682
	C_{CT_map} in basal	0.944	9	0.623	0.917	10	0.329
	C_{CT_map} in anterior	0.971	9	0.903	0.847	10	0.054
	C_{CT_map} in posterior	0.939	9	0.568	0.926	10	0.411
	C_{CT_map} in right	0.955	9	0.741	0.934	10	0.486
	C_{CT_map} in left	0.946	9	0.641	0.888	10	0.161
	R_{A-B}[#]	**0.821**	**9**	***0.036***	**0.844**	**10**	***0.049***
	R_{A-P}[#]	0.901	9	0.257	**0.844**	**10**	***0.049***
	R_{R-L}	0.895	9	0.225	0.912	10	0.294
	R^2 for P-V fitting	0.951	9	0.706	0.937	10	0.523
	Kurtosis	0.945	9	0.637	0.962	10	0.808
	Skewness	0.891	9	0.204	0.927	10	0.414
Histology	Septal wall thickness	0.919	10	0.348	0.887	10	0.157

[#] Parameters that are not normally distributed.

Supplementary Data 4: Cross-validation of histological analysis

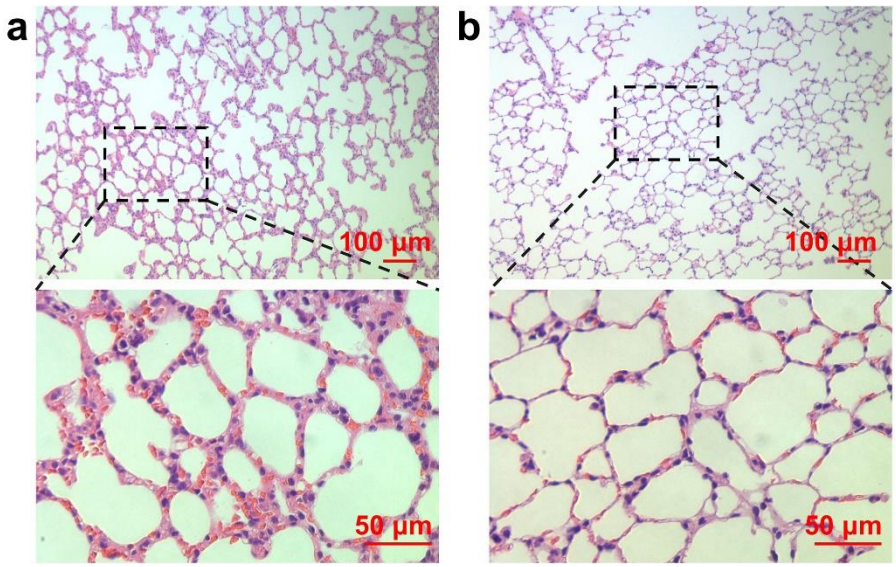

Fig. S3. Typical hematoxylin and eosin (H&E) stained histopathology. (a) fibrosis rat and (b) control rat. The sections from the fibrosis rat showed clear thickening of the alveolar septa compared to the control rat (Top: scale bar = 100 µm, bottom: scale bar = 50 µm).

Supplementary Data 5: Relation between of C_{Xe} and C_{Xe_map} measurement

In C_{Xe} calculation, changes in lung volume are obtained through segmentated ventilation images, while changes in lung volume in C_{Xe_map} are derived from Jacobian determinant maps after registration. To validate the consistency between the two parameters, we evaluated the correlation between C_{Xe} and the sum of C_{Xe_map}, as shown in Fig. S4. The results indicate a good consistency between the two parameters (r = 0.838).

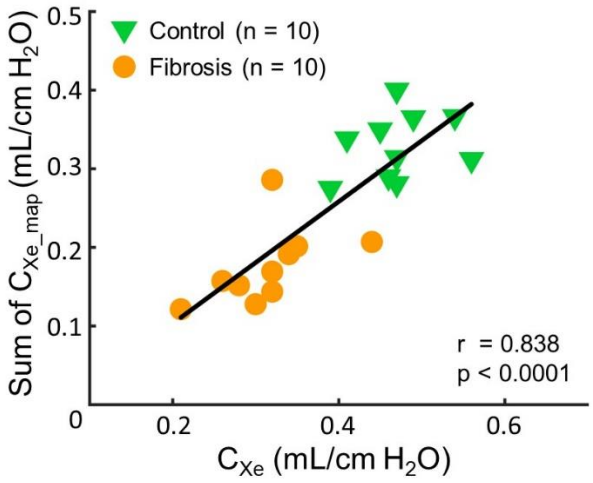

Fig. S4. The correlation between C_{Xe} and the sum of C_{Xe_map}.