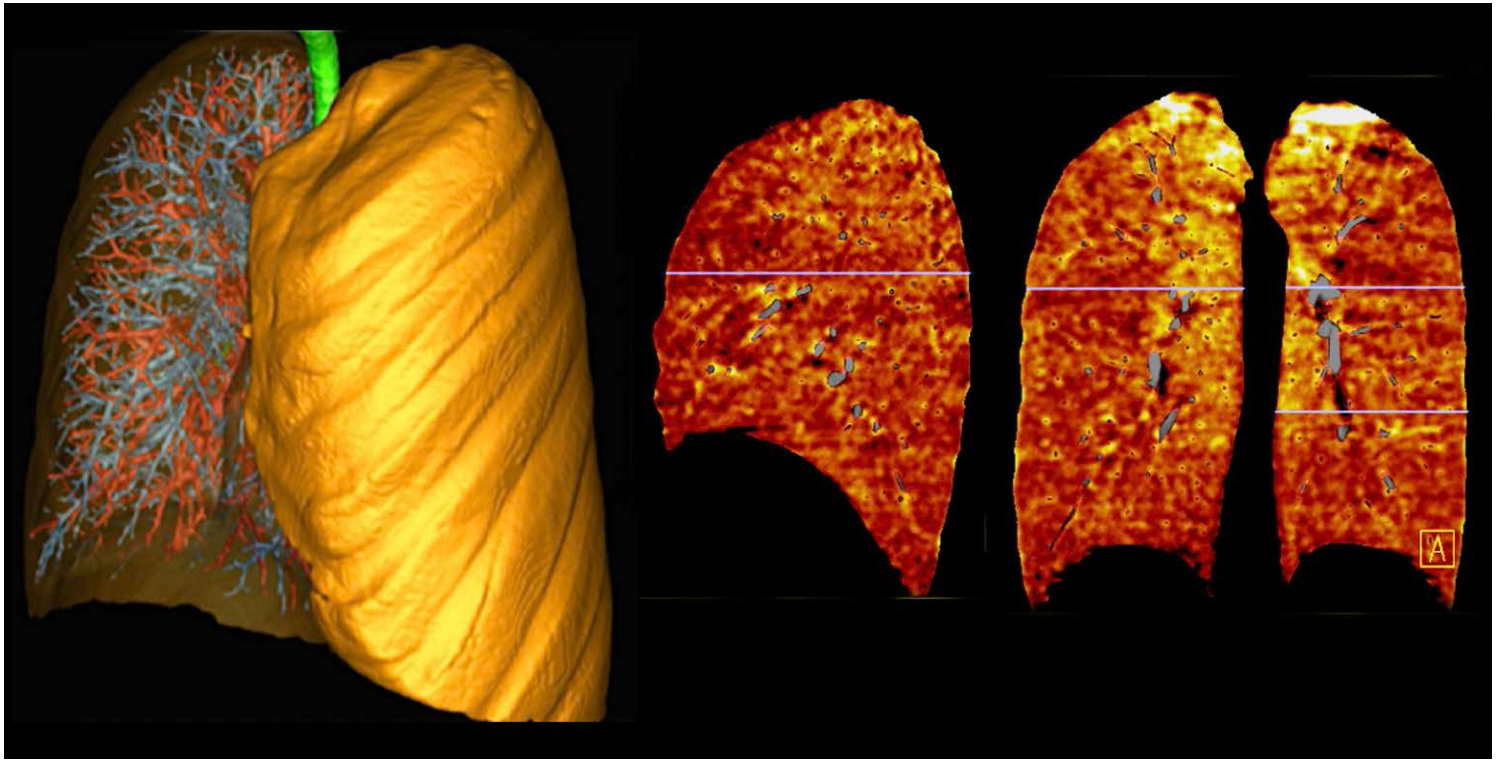
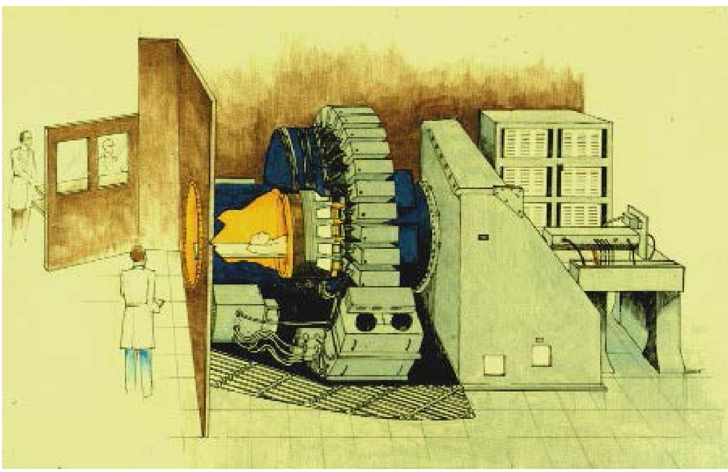
CT and MRI Serving to Provide Lung Structure-Function Relationships for the Phenotyping of Lung Disease

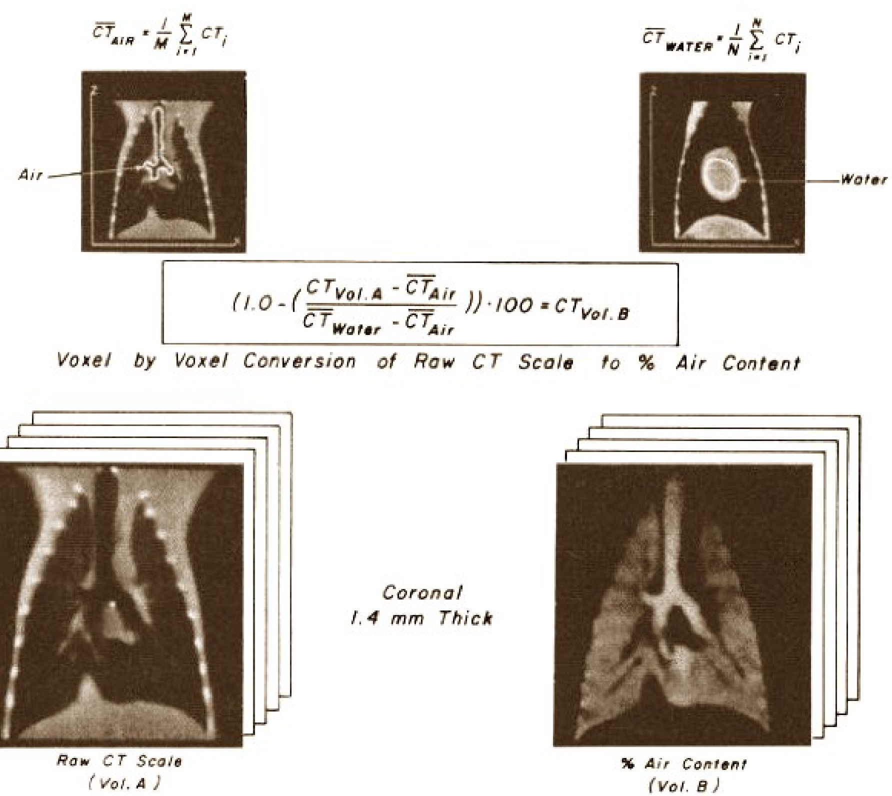
Eric A. Hoffman, PhD
University of Iowa, Iowa City, Iowa
Advanced Pulmonary Physiomic Imaging Laboratory (APPIL)



EAH is a founder of and share holder in VIDA Diagnostics

Earliest Dynamic Volumetric CT Prototype: 1974 SSDSR Dynamic Spatial Reconstructor (DSR) Installed 1979 Mayo Clinic

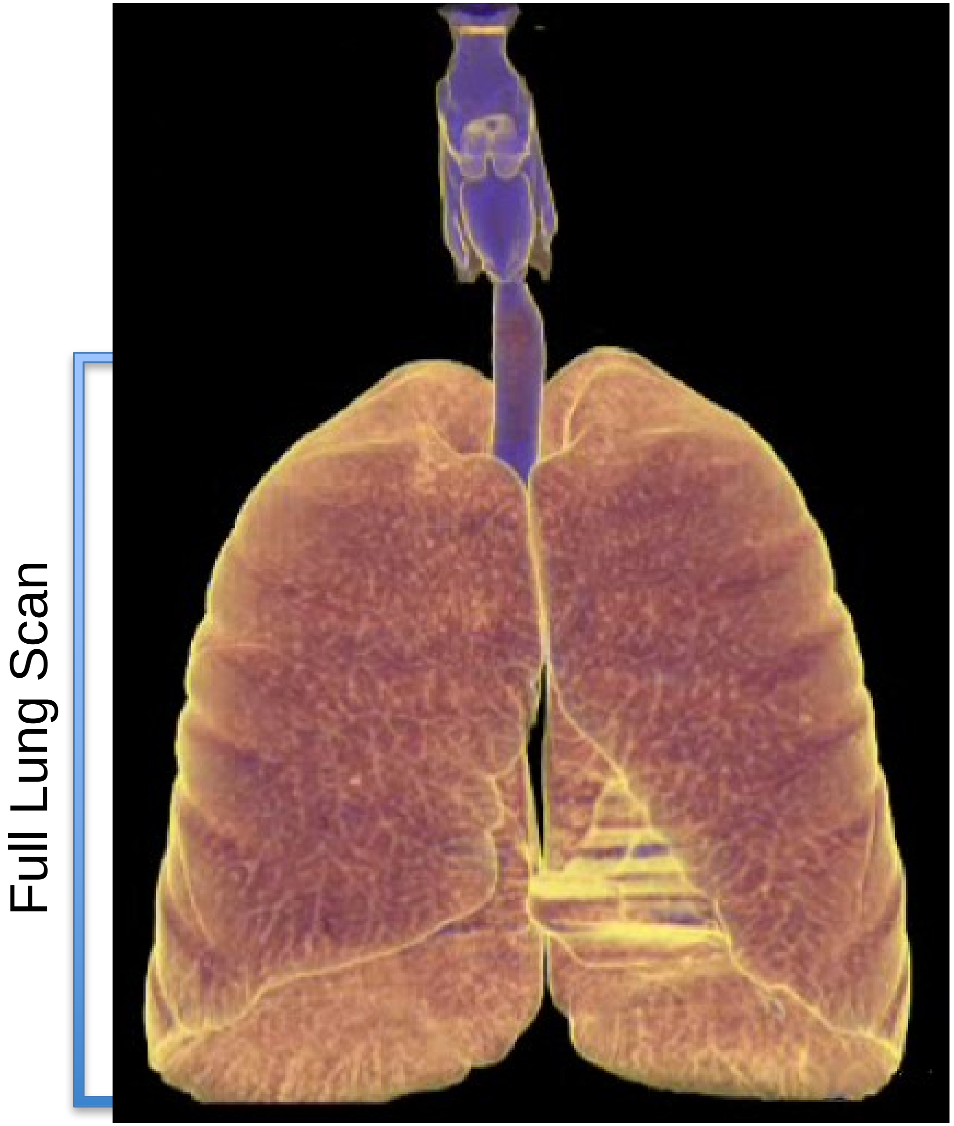




Hoffman EA. JAP 59:468-480, 1985

Standardized Volumetric Lung Imaging

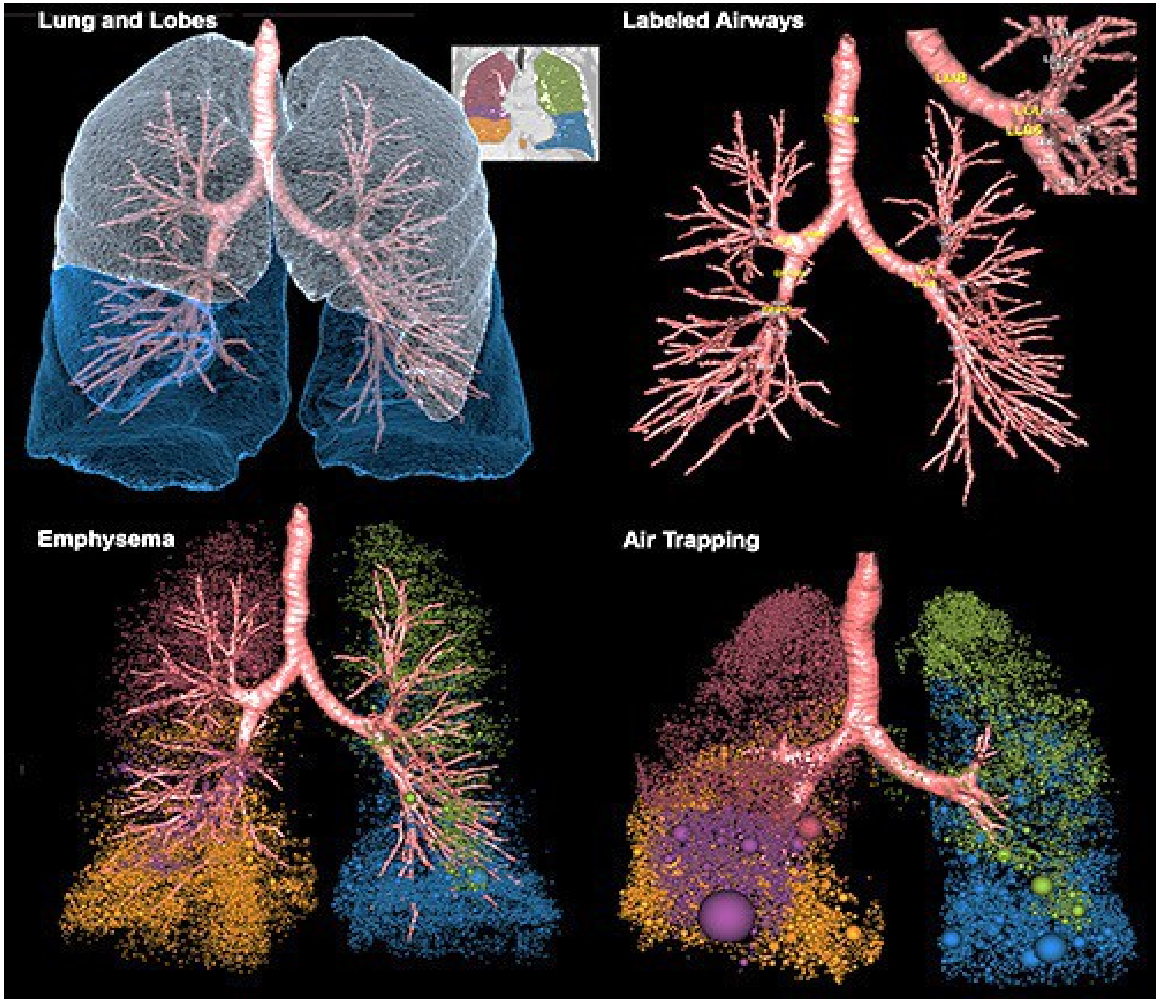
- Coached Lung Volume (TLC, FRC, RV)
- Standardized kV and CTDIvol
- Standardized Scanner Specific Reconstruction Kernel
- Standardized Slice Thickness and Spacing



Sieren JP et al; Am J Respir Crit Care Med. 2016 Oct 1;194(7):794-806.

Quantitative CT Assessment

Coached
TLC and RV



Voxels < -950HU
TLC

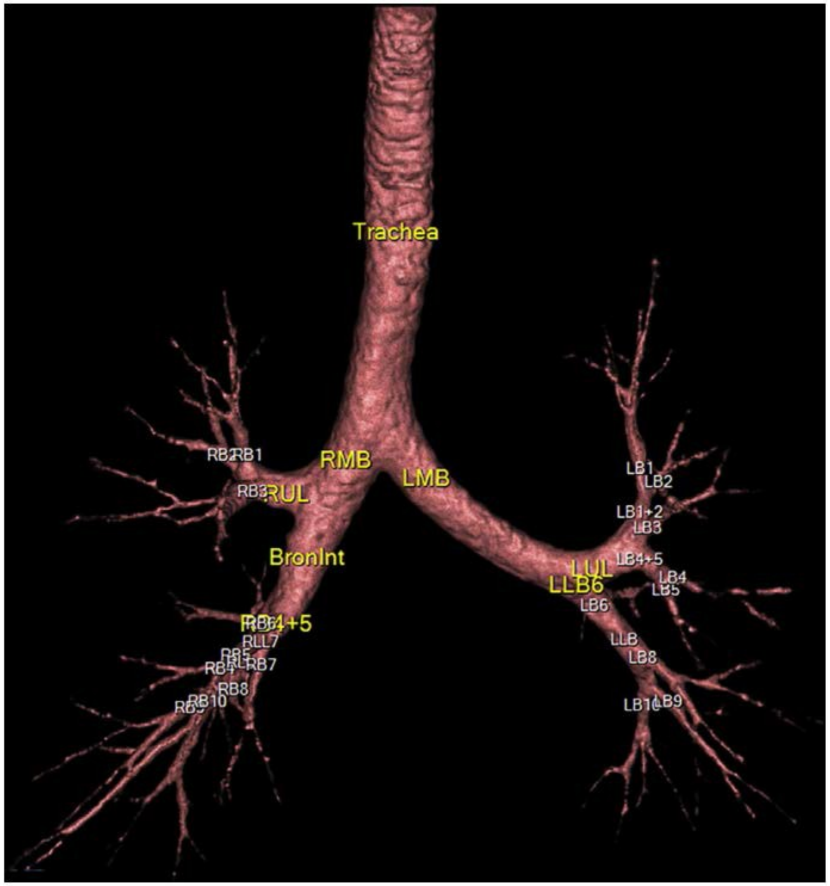
Voxels < -856HU
RV

$$HU = 1000 \times \frac{\mu - \mu_{\text{water}}}{\mu_{\text{water}} - \mu_{\text{air}}}$$

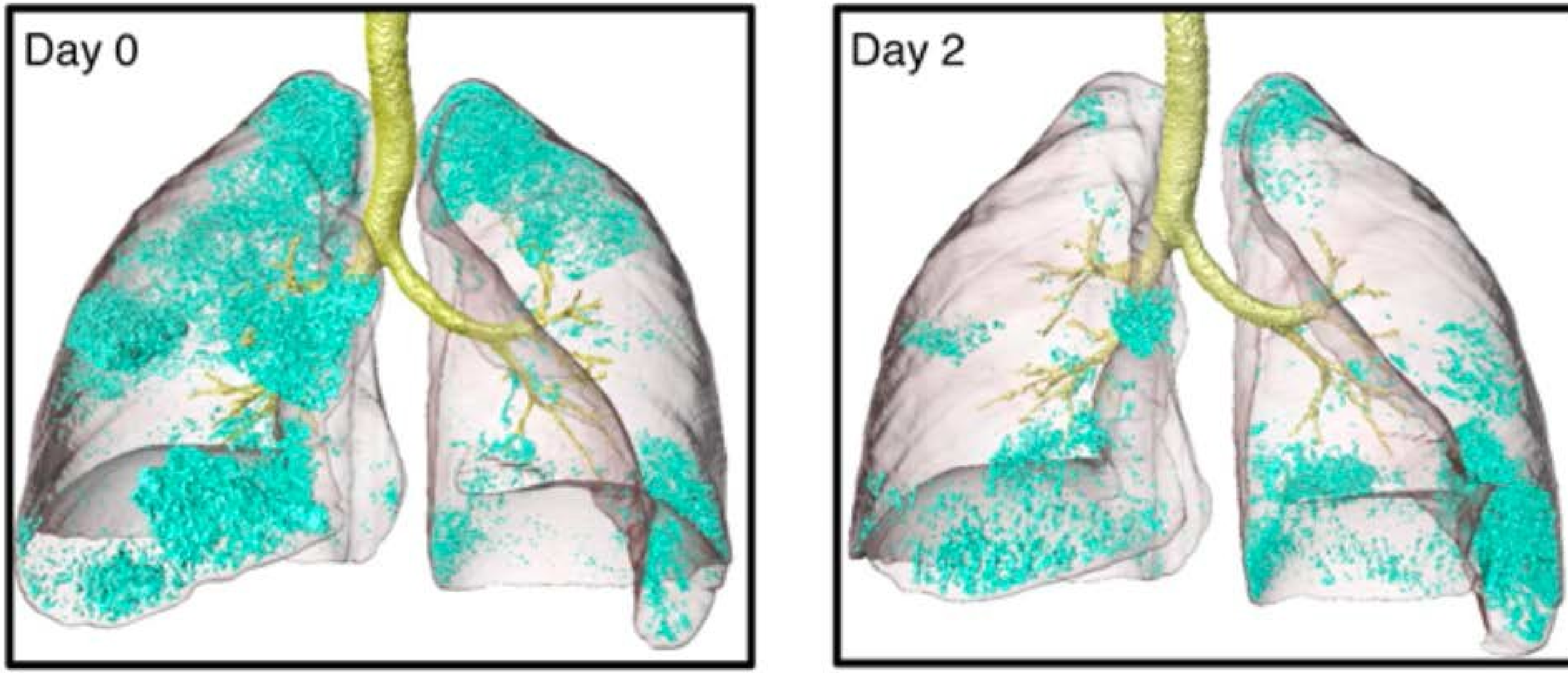
APPIL

Overview – Quantitative CT

- Density
  - Emphysema like lung: voxels <-950HU at TLC
  - Air-Trapping = voxels <-856HU at FRC or RV
  - Parametric Response Mapping
  - Disease Probability Measures
  - Indices of Regional Mechanics (Jacobians, ADI etc.)
  - Texture analysis
- Airway Segmentation
  - Wall thickness/area
  - Lumen area, Hydraulic Diameter
  - Eccentricity
  - Global and path specific Pi10
- Functional (DECT)
  - ventilation and perfusion



Ivacaftor Reduces CT-assessed Air trapping In CF Patients with G551D-CFTR Mutation



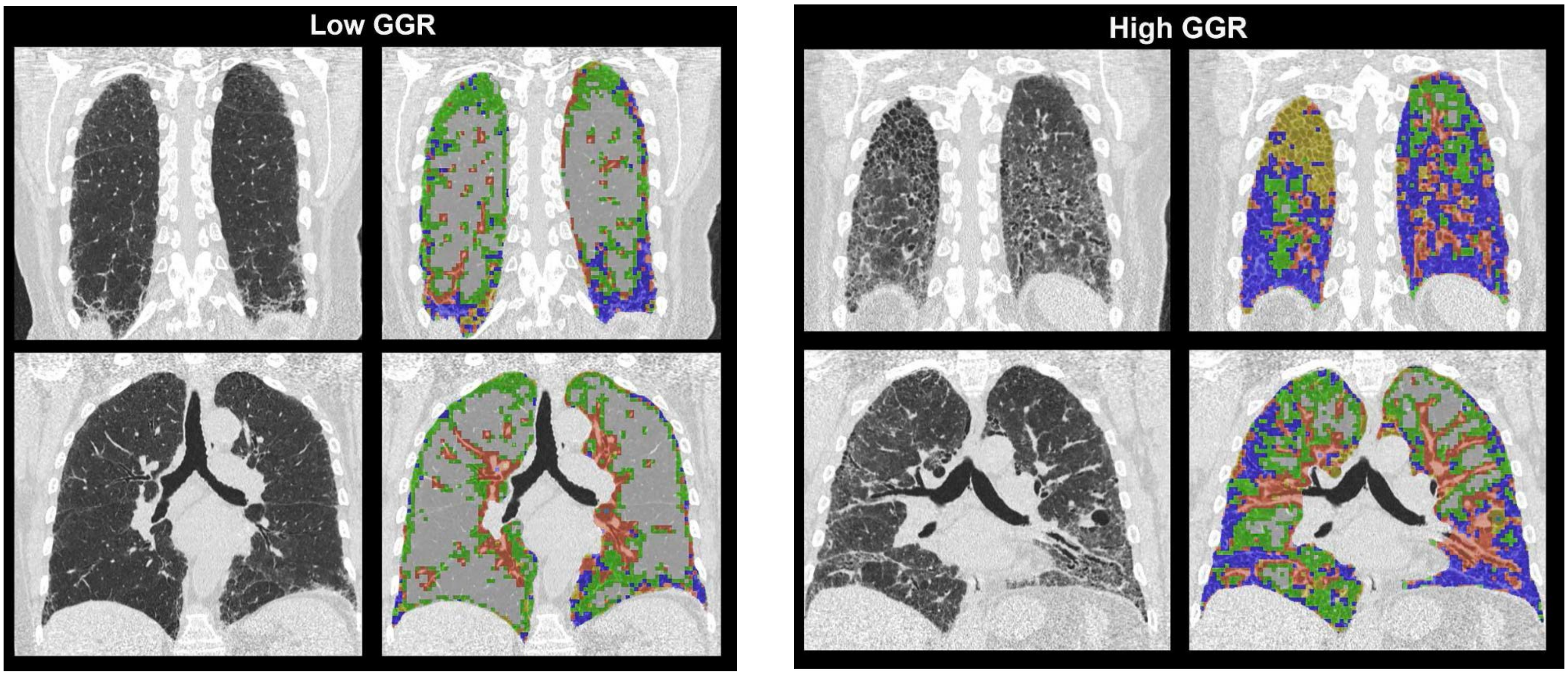
ivacaftor stimulates G551D-CFTR* function.

*CFTR: Cystic fibrosis transmembrane conductance regulator

Adam RJ et al. JCI Insight. 2016 Apr 7;1(4):e86183.

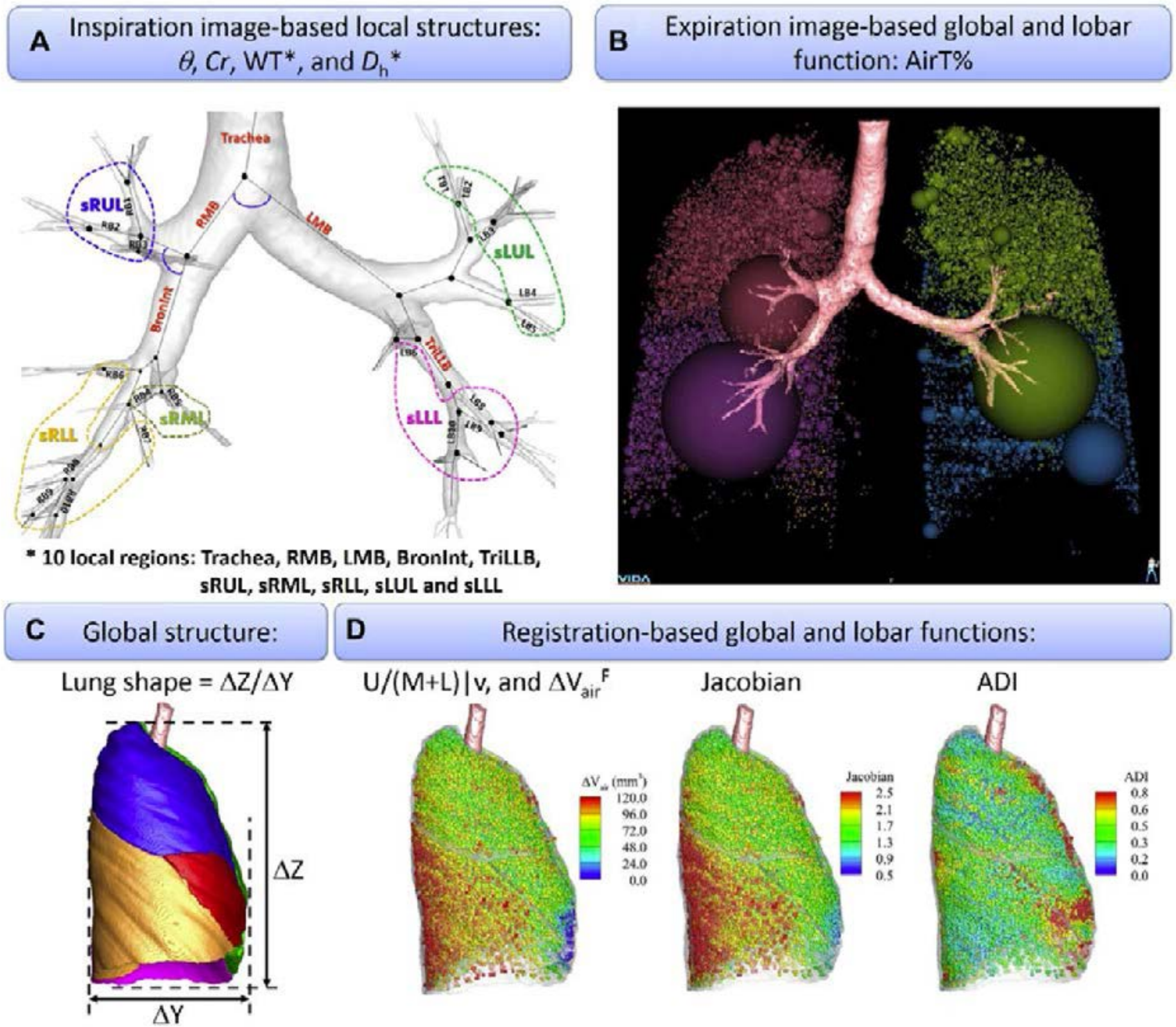
Texture-based Parenchymal Characterization
AMFM Aids IPF Prognostication

Increased GGR at baseline was associated with increased risk of IPF progression



Salisbury ML et al. Am J Respir Crit Care Med. 2017 Apr 1;195(7):921-929.

QCT-based Clustering Differentiates Asthmatic Subgroups



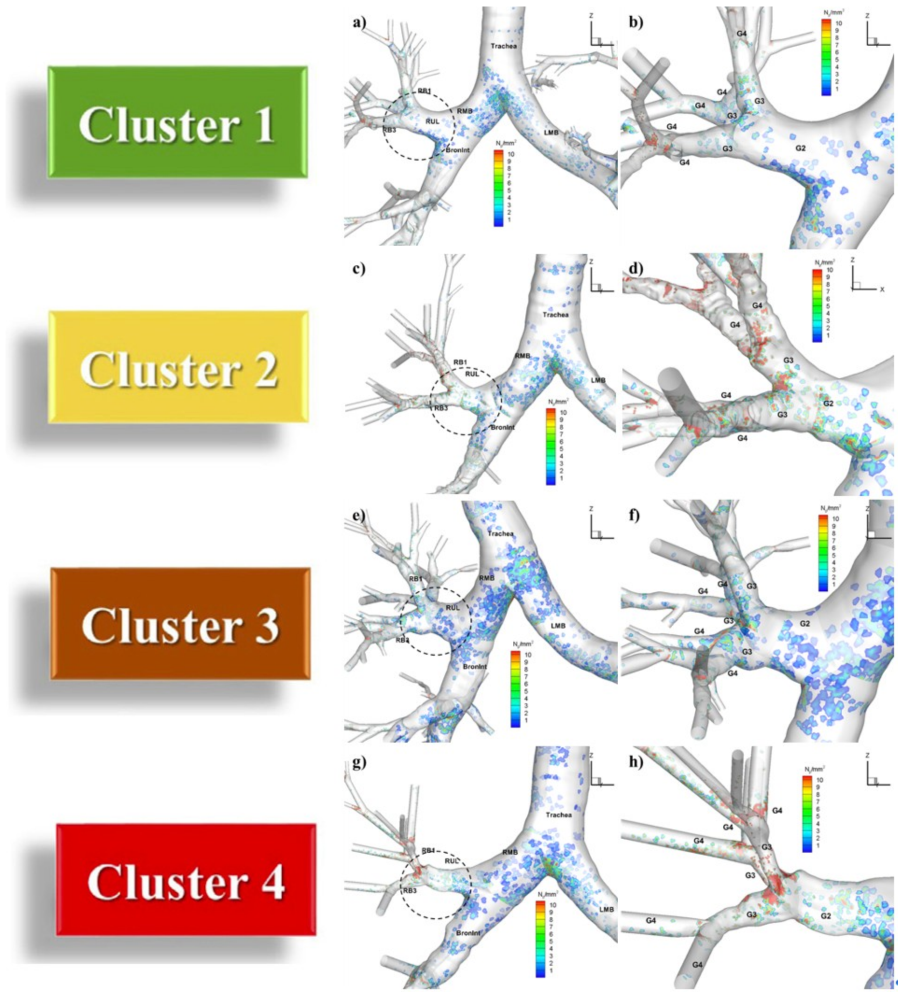
Choi S et al. J Allergy Clin Immunol. 2017 Jan 28 (e-pub)

Clusters are Associated with Distinctive Clinical Phenotypes

	Imaging characteristics	Clinical characteristics
Cluster 1	• Normal airway structure • Increased lung deformation (Jacobian and ADI↑)	• Younger, early onset • Nonsevere asthma • Reversible lung function • Easy to control asthma symptoms
Cluster 2	• Airway luminal narrowing (D_h*↓) • No airway wall thickening (WT*) • Significant reduction of lung deformation (Jacobian and ADI↓)	• Nonsevere and severe asthma • Persistently altered lung function • Marginal to no inflammation • Difficult to control asthma symptoms
Cluster 3	• Airway wall thickening (WT*↑) • No airway luminal narrowing (D_h*) • Moderate reduction of lung deformation (Jacobian and ADI↓)	• Obese, female-dominant • Severe asthma • Reversible lung function • Blood lymphopenia • Difficult to control asthma symptoms
Cluster 4	• Airway luminal narrowing (D_h*↓) • Significant reduction of lung deformation (Jacobian and ADI↓) • Significant air-trapping (AirT%↑)	• Older, late onset, male-dominant • Severe asthma • Persistently altered lung function • Neutrophilic-dominant inflammation • Difficult to control asthma symptoms

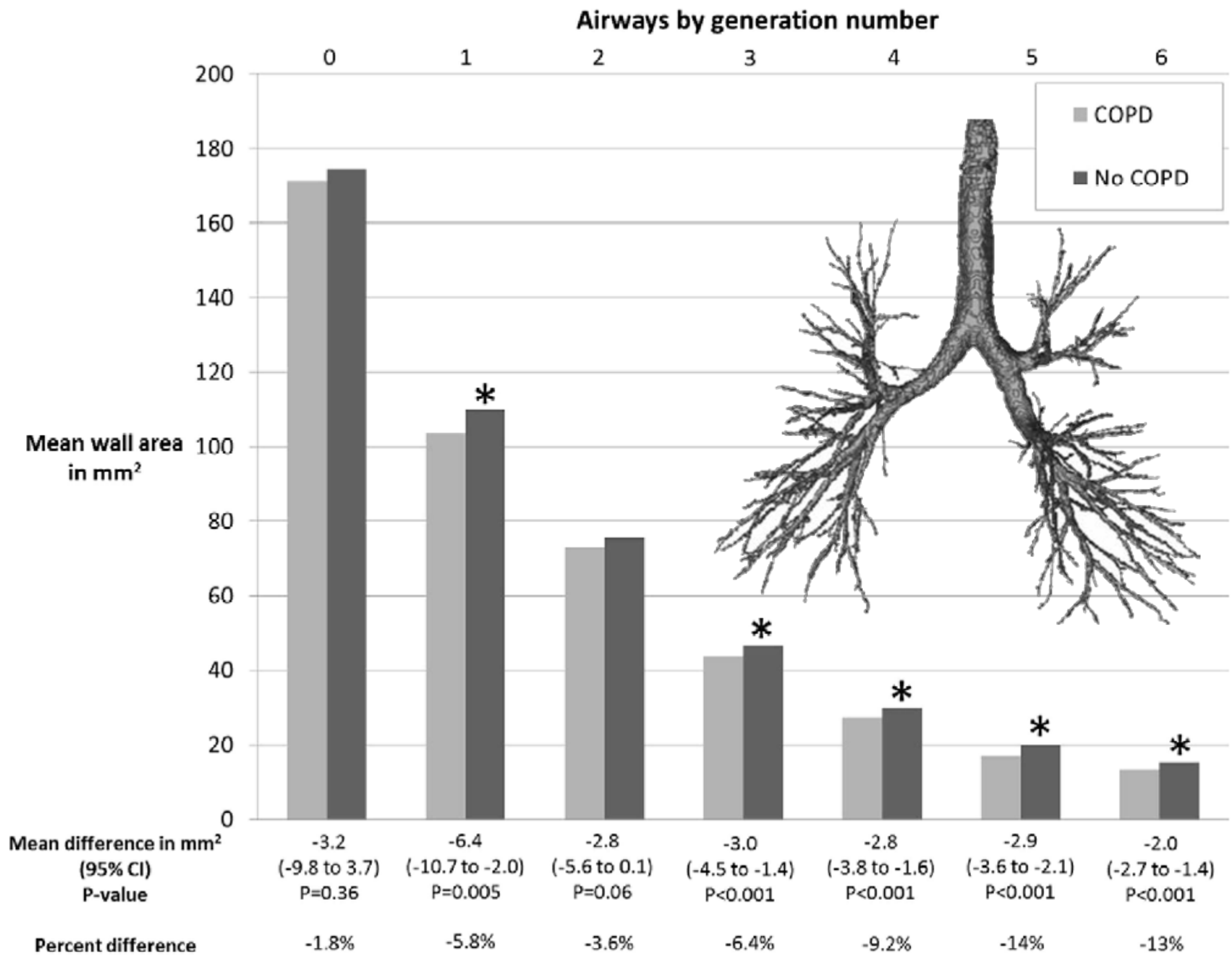
Choi S et al. J Allergy Clin Immunol. 2017 Jan 28 (e-pub)

CFD: Reduced Particle Deliver To Periphery in Clusters 2 and 4



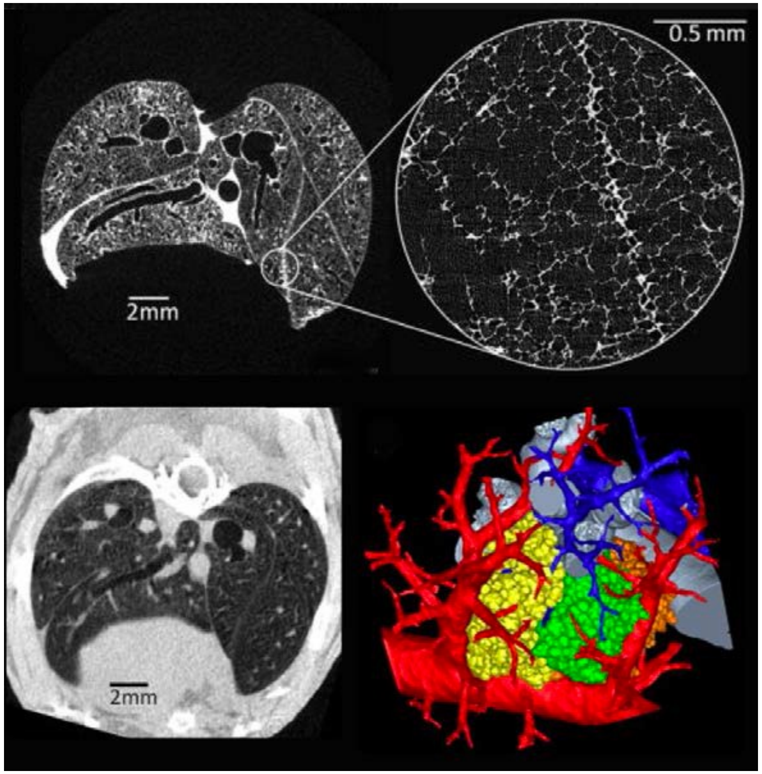
Choi J, et al. J Aerosol Med Pulm Drug Deliv. 2019 Aug;32(4): 213-223.

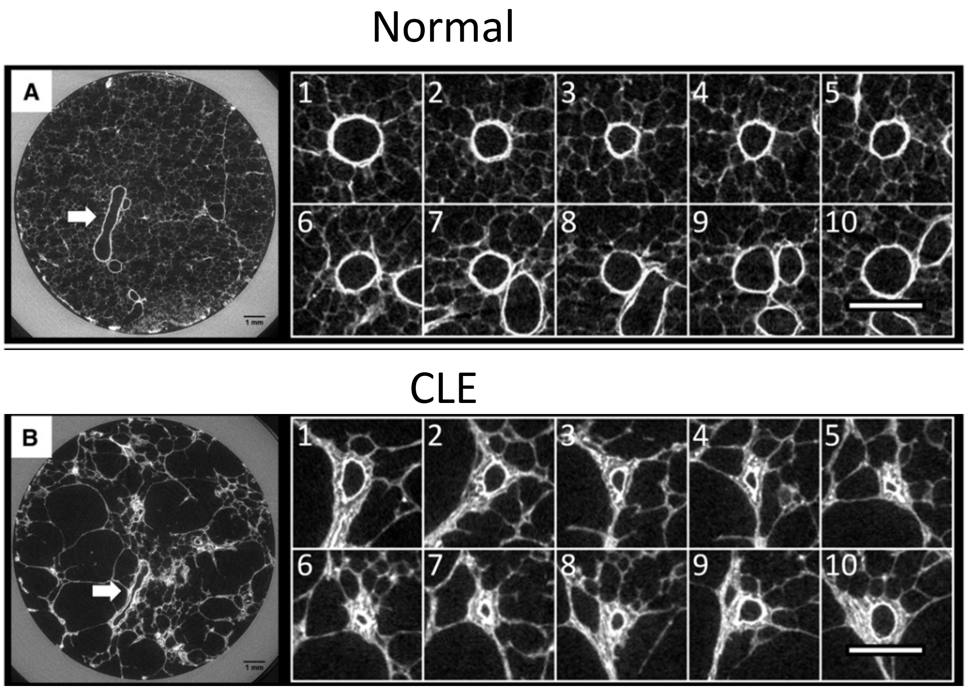
Thinner Airway Walls in COPD If Comparisons are Spatially Matched



Smith BM et al. Thorax. 2014 Nov;69(11):987-96.

Multi-Scale Imaging via Micro CT





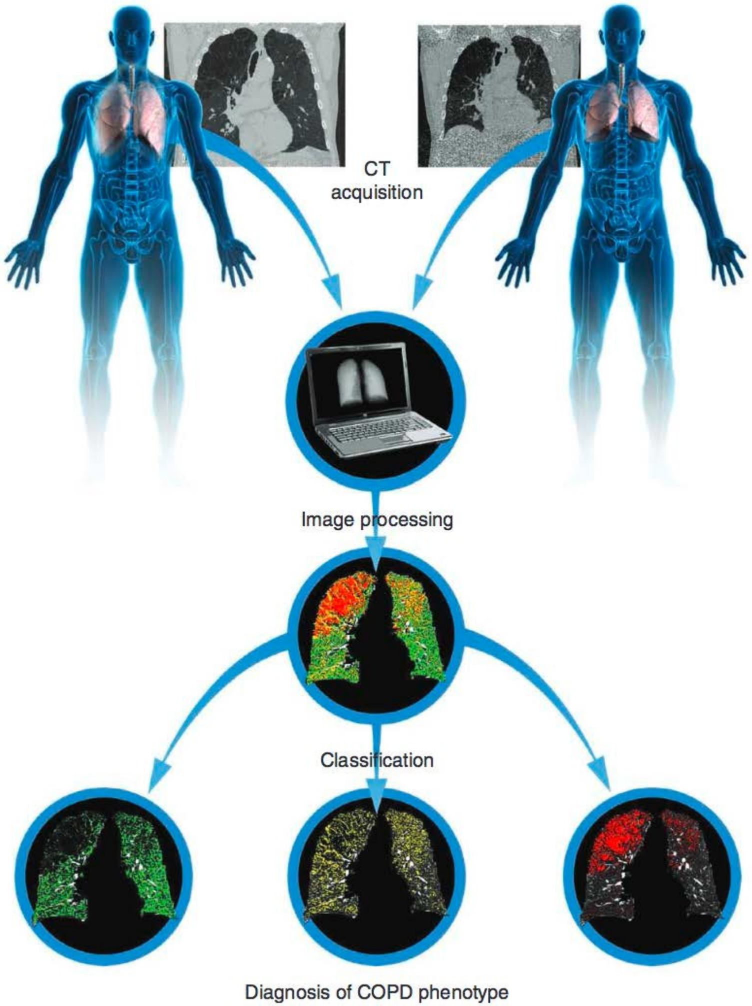
Despite pre-terminal bronchial wall thickening. However, in CLE, wall volume was decreased.

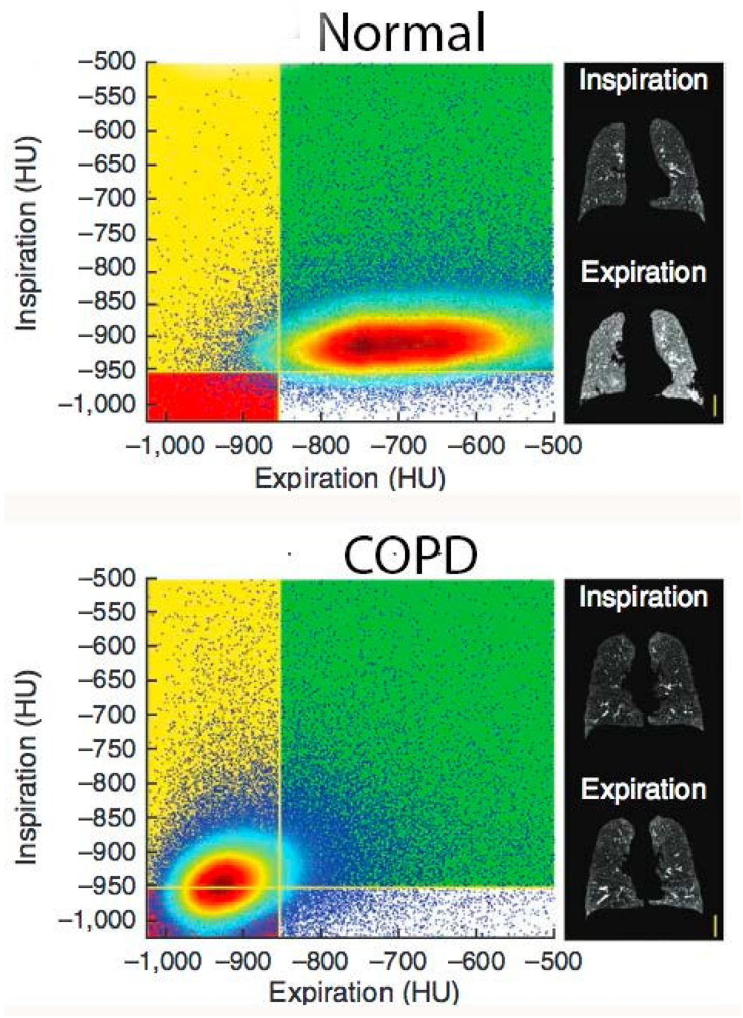
Vasilescu D et al. Proc Natl Acad Sci U S A. 2012 Oct 16;109(42):17105-10.

Tanabe N et al. Am J Respir Crit Care Med. 2017 Mar 1;195(5):630-638.

APPIL

Parametric Response Map:
Characterizing Functional Small Airways Disease (fSAD)

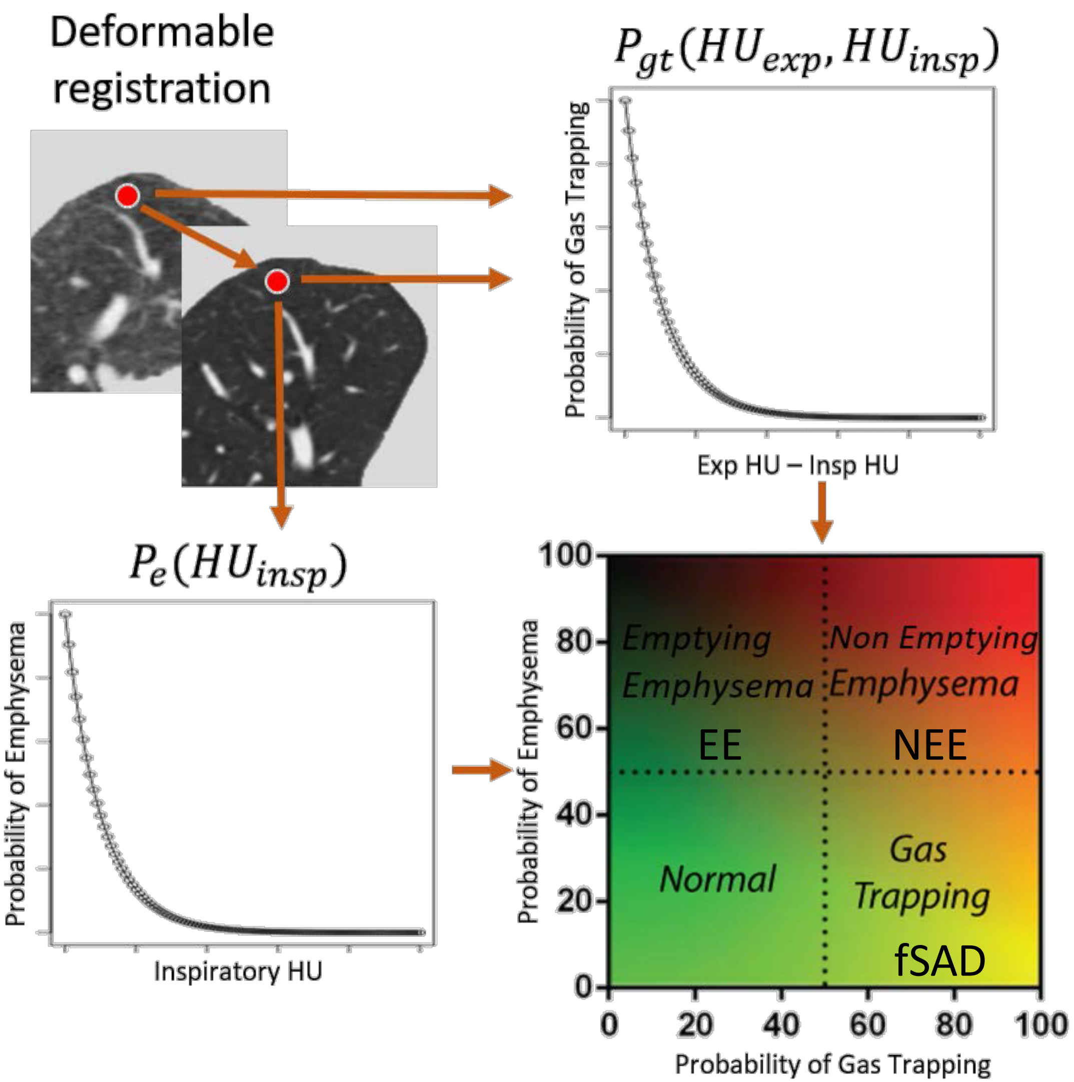




Galbán CJ et al. Nat Med. 2012 Nov;18(11):1711-5.

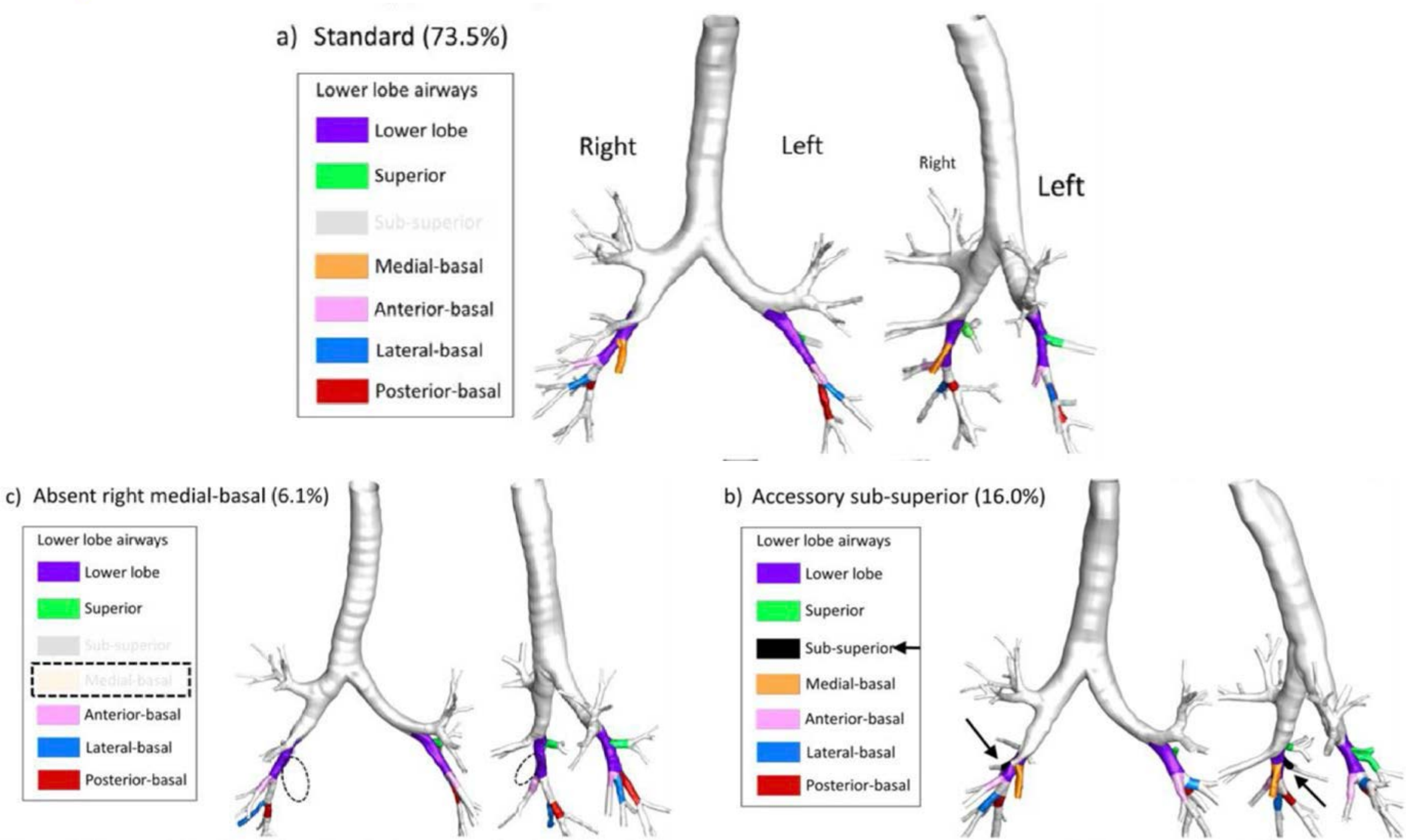
Disease Probability Map

Assign probabilities to voxels based on TLC/RV differences



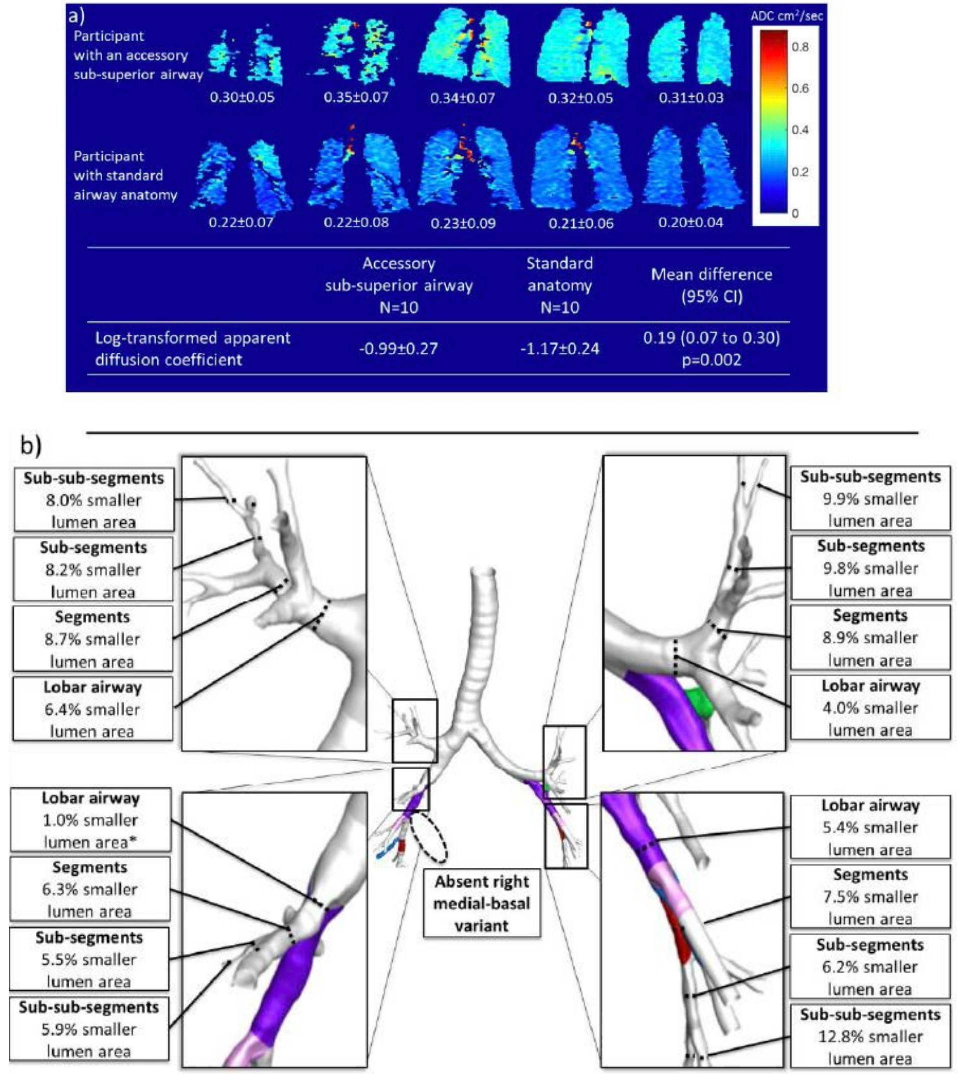
Kirby M, et al. Respiration.2017;94(4):336-345.

Airway Variants Associated with Increased Risk of COPD



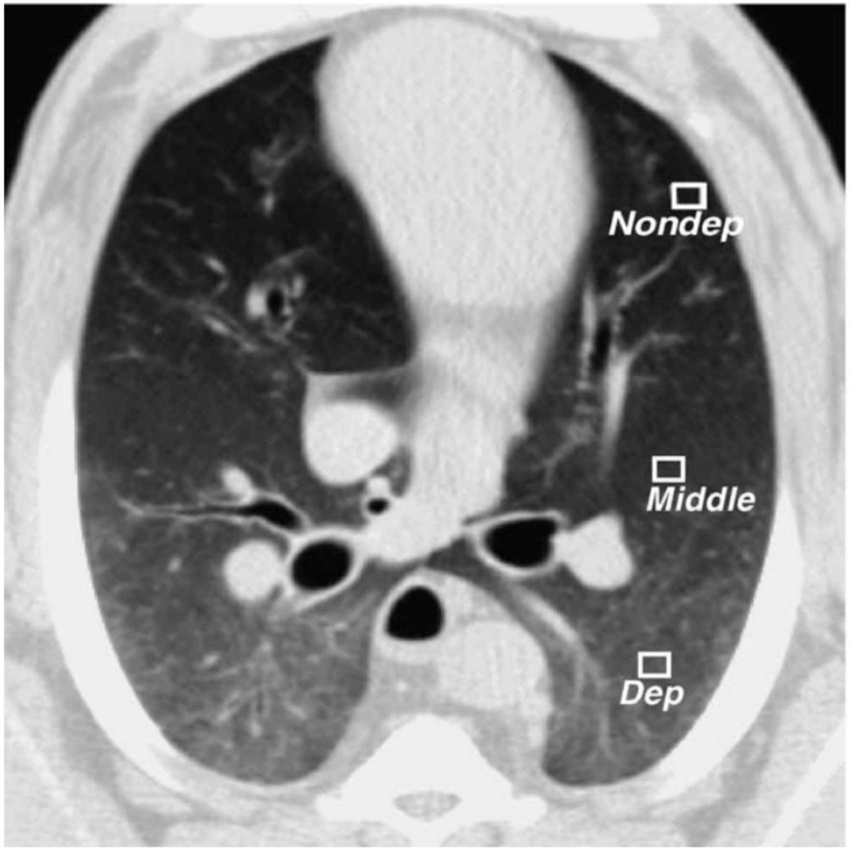
Smith BM et al. Proc Natl Acad Sci U S A. 2018 Jan 30;115(5):E974-E981.

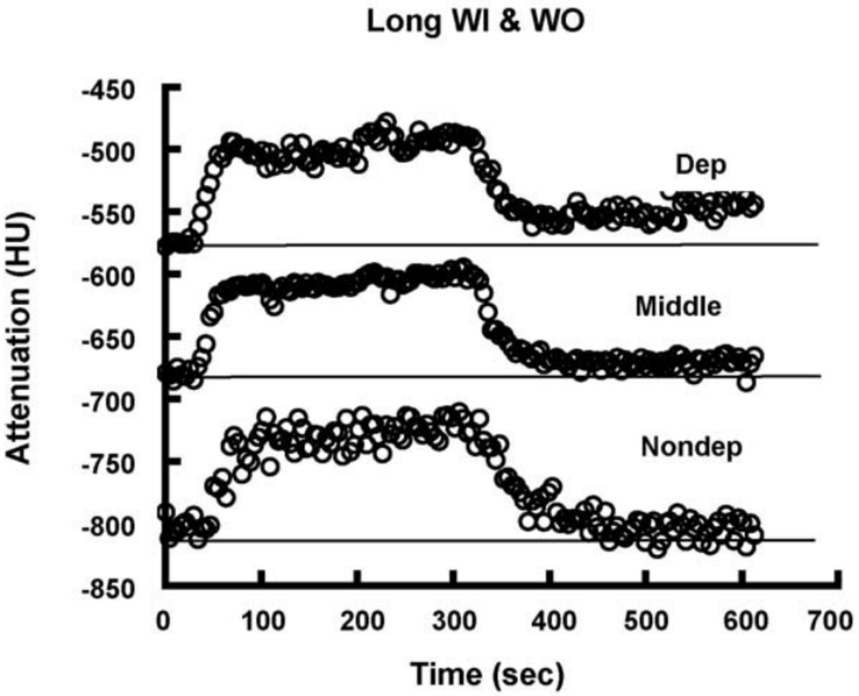
Airway Variants Are Indicative of Global Changes in Lung Structure



Smith BM et al. Proc Natl Acad Sci U S A. 2018 Jan 30;115(5):E974-E981.

Xenon Imaging for Regional Ventilation



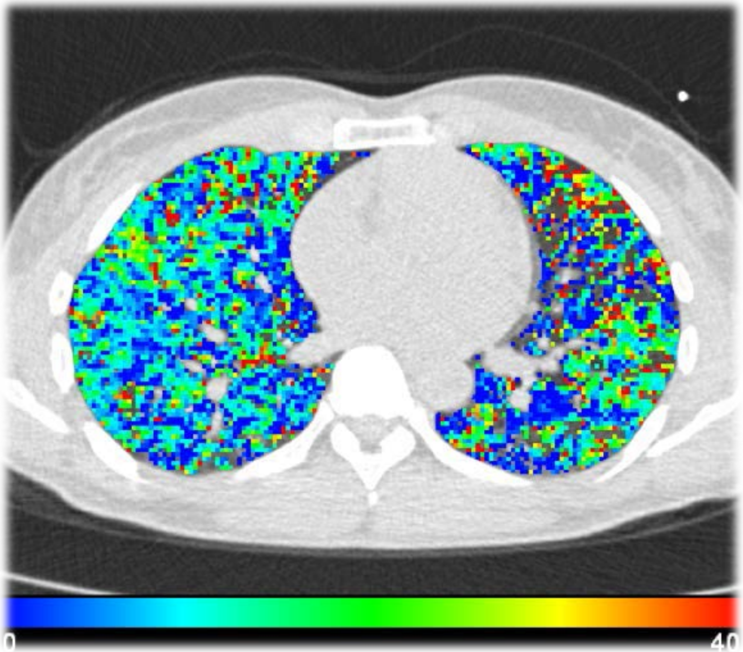


Chon D et al. Respir Physiol Neurobiol. 2005; 148:65-83

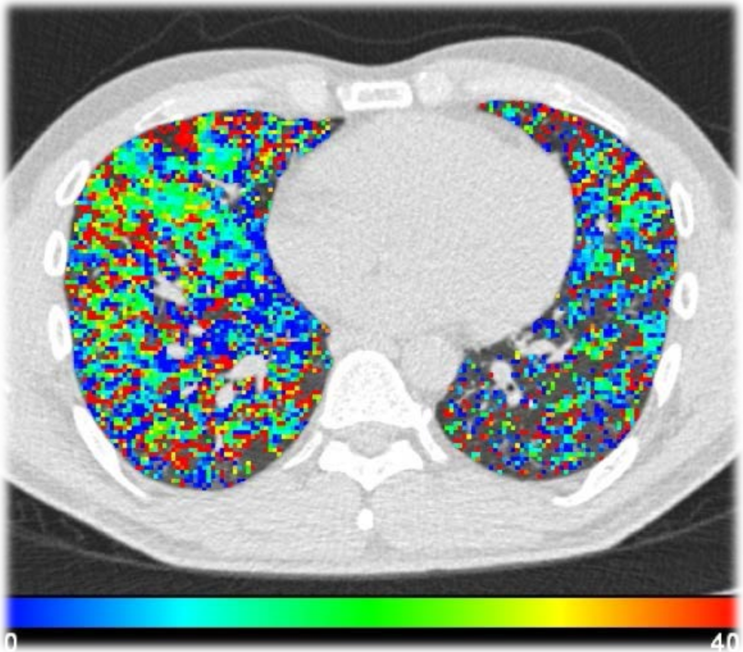
APPIL

Evidence of Heterogeneous Ventilation in Smokers

Non-Smoker



Smoker

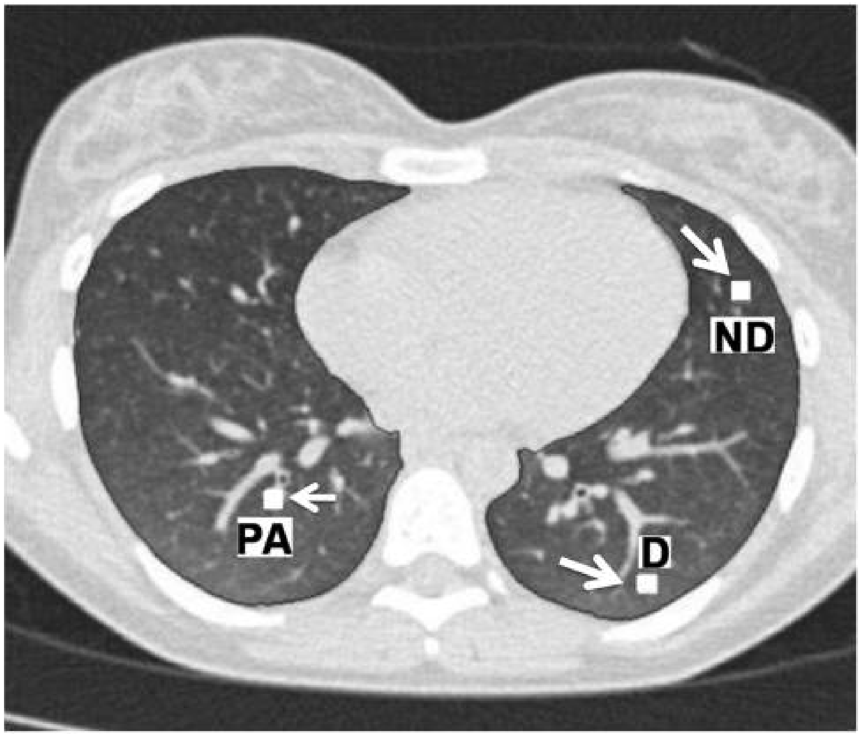


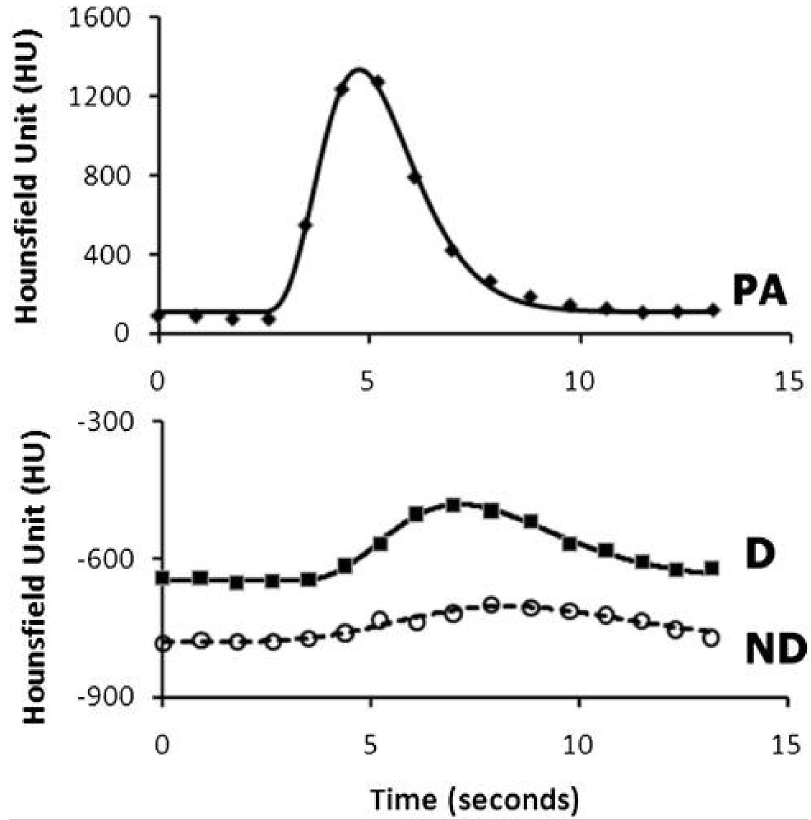
Percentage of lung that does not curve fit

- **Non-Smoker (N=10)** **23.78% w/o Fit**
- **Smoker (N=3)** **40.71% w/o Fit**

M Fuld, EA Hoffman et al. ATS. 2009 San Diego, Abst 3530

First Pass Kinetics for Assessment of Regional PBF via Dynamic Axial CT

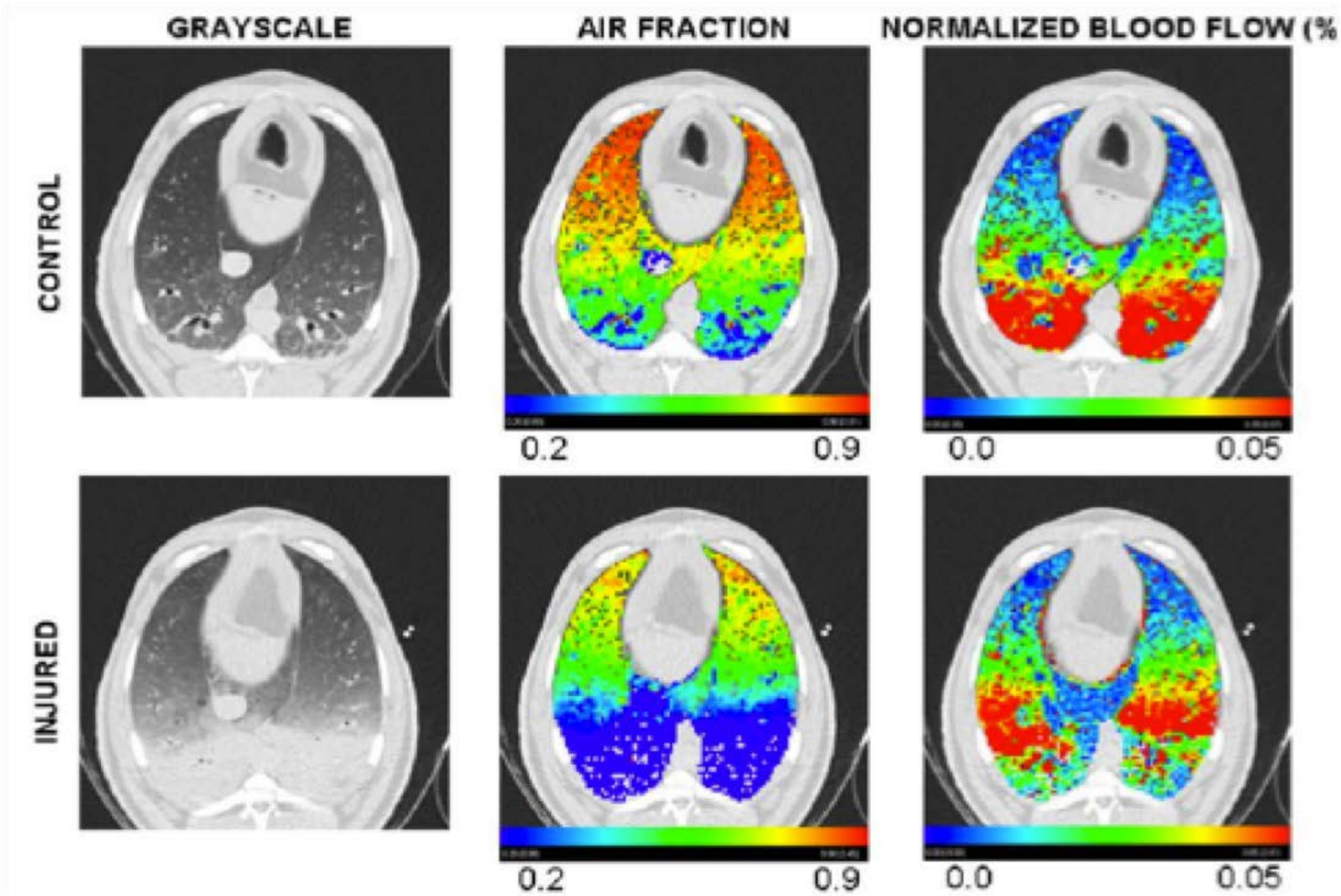




Hoffman EA, Tajik JK, Kugelmass SD. Comput Med Imaging Graph. 1995 Jan-Feb;19(1):101-12.
Hoffman EA, Chon D. Proc Am Thorac Soc. 2005;2(6):492-8, 506.

Saline Lavage:Hypoxia-based Blood Flow Redistribution

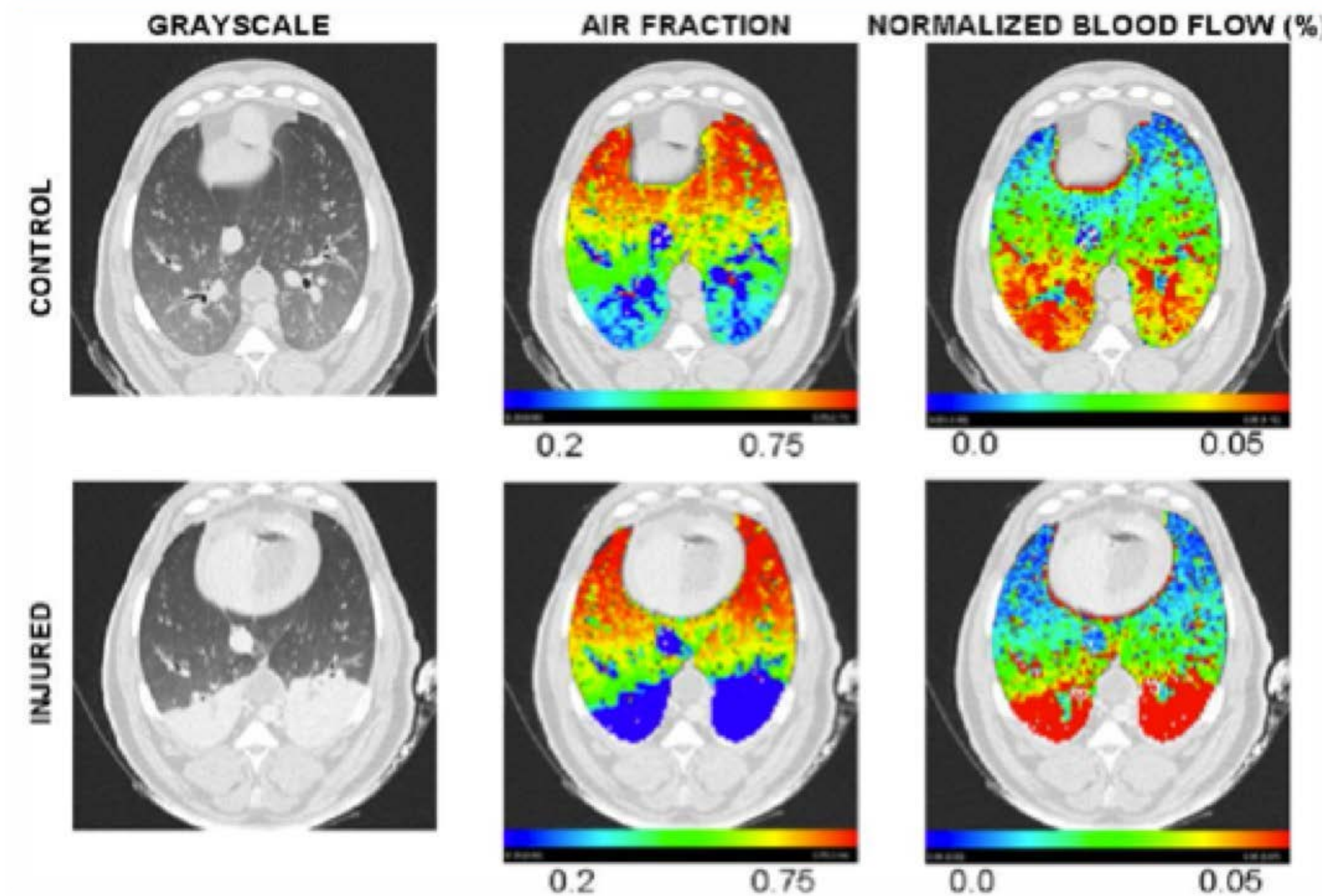
Hypoxic Pulmonary Vasoconstriction: Intact



RB Easley et al. Acad. Radiol. 2006 July; 13(7): 916-21.

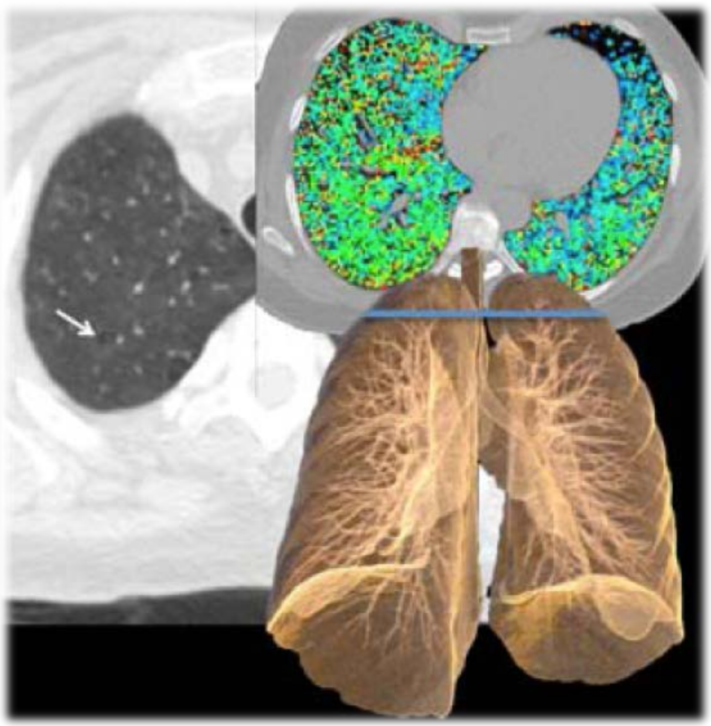
LPS Injury: Inhibition of Hypoxia-based Blood Flow Redistribution

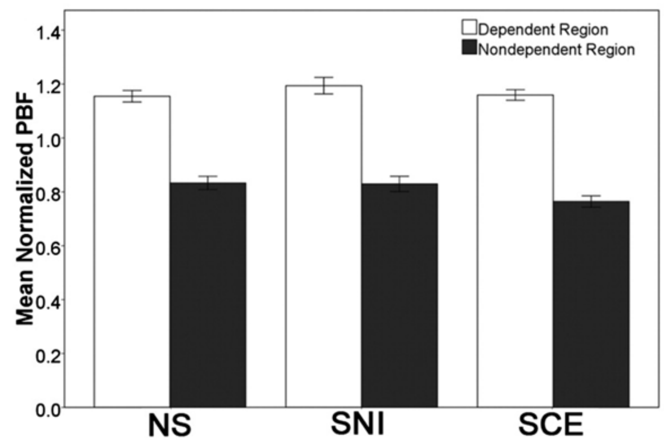
Hypoxic Pulmonary Vasoconstriction: Blocked

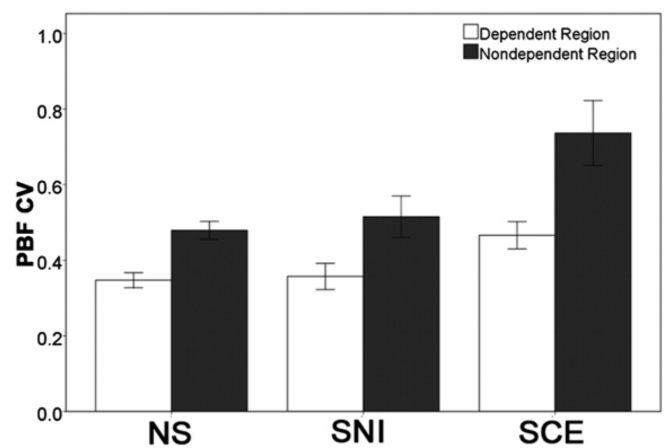


RB Easley et al. Acad. Radiol. 2006 July; 13(7): 916-21.

Centriacinar Emphysema in Normal Smokers Associated with Increased Perfusion Heterogeneity

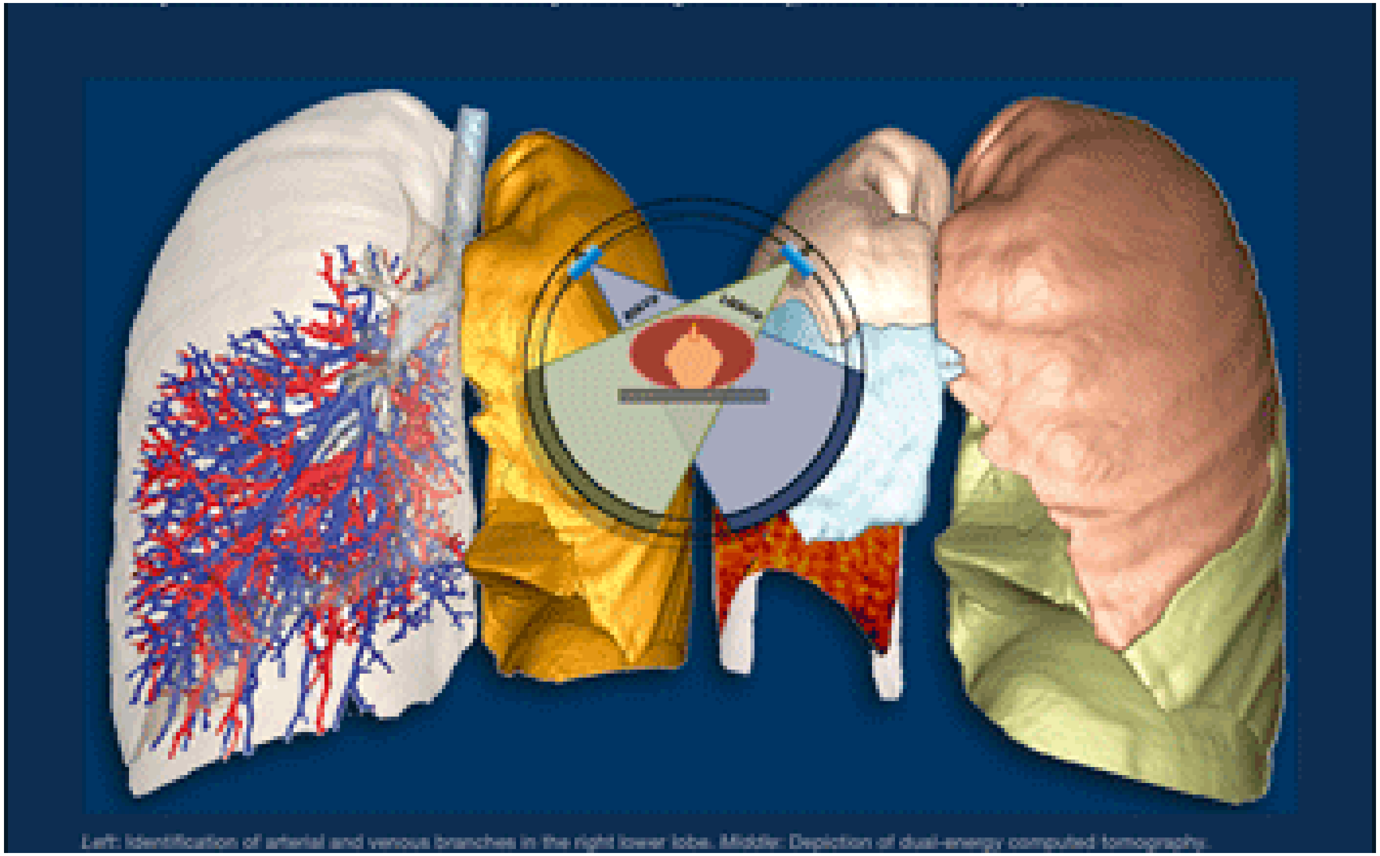






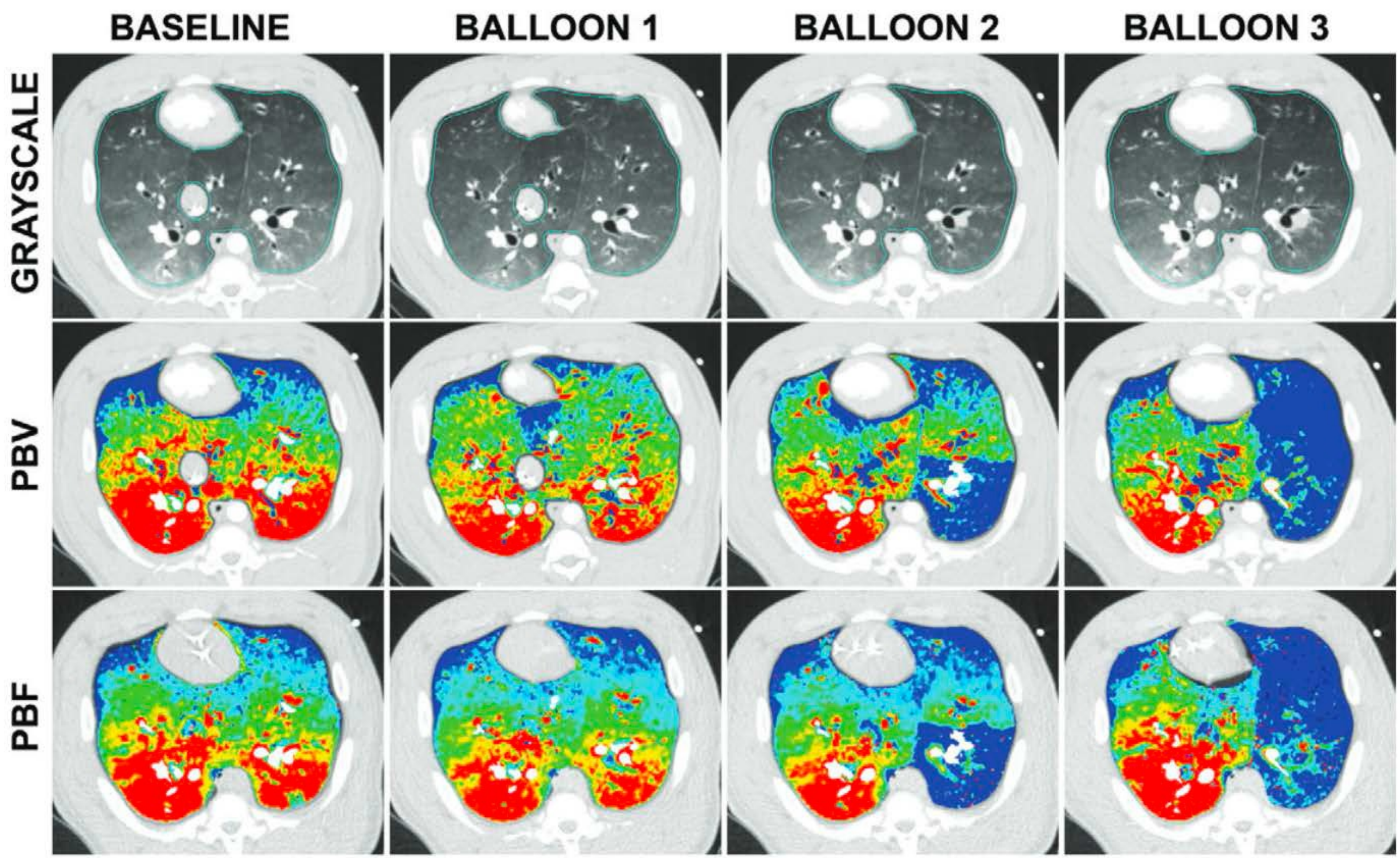
Alford et al., Proc Natl Acad Sci U S A. 2010 Apr 20;107(16):7485-90

Dual Energy Computed Tomography
DECT



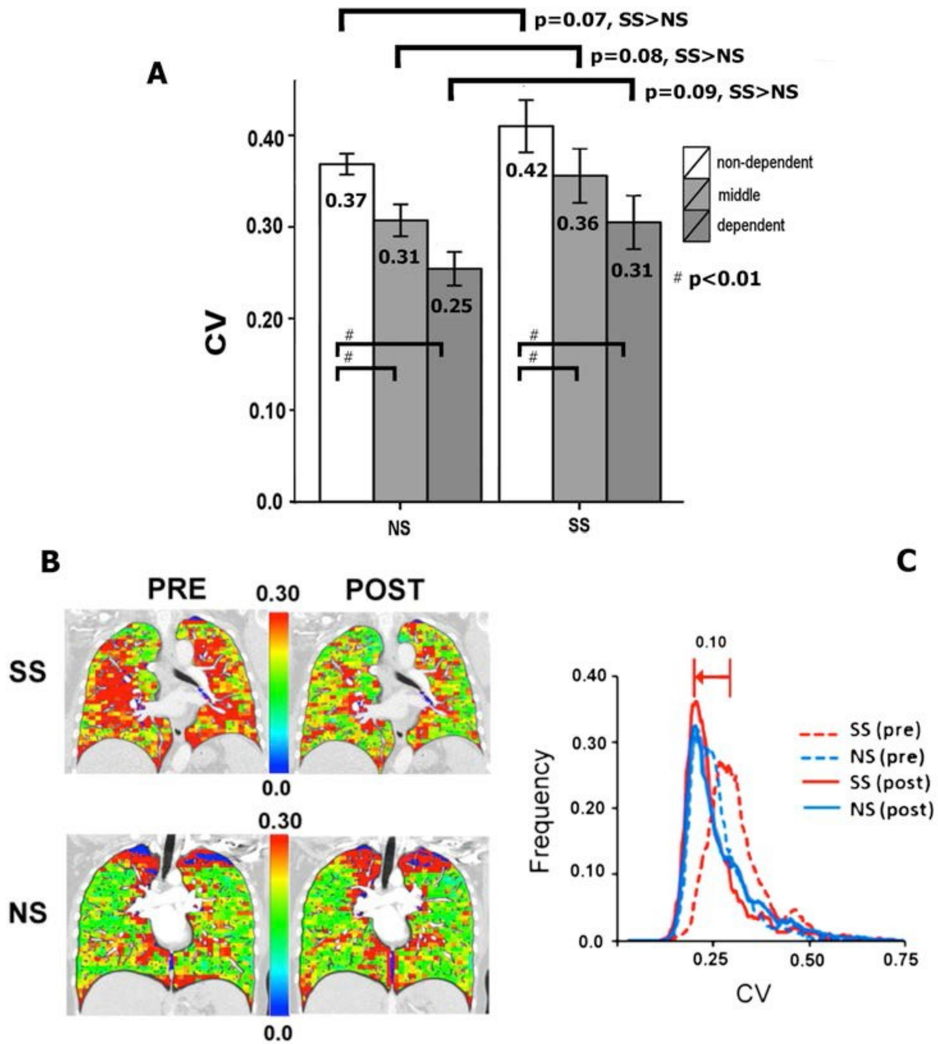
Iyer et al : Am J Respir Crit Care Med. 2016 Mar 15;193(6):652-61

Dynamic PBV vs. DECT-derived PBV
Porcine Model: PA Balloon



Fuld et al. Radiology. 2013 Jun;267(3):747-56.

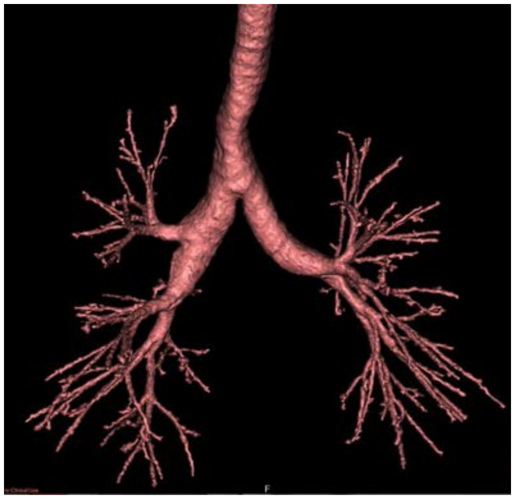
Increased PBV-CV in Emphysema Susceptible Smokers Reversed by Sildenafil



Iyer et al : Am J Respir Crit Care Med. 2016 Mar 15;193(6):652-61

What about dose?

SOMATOM Force: ~10 Fold Radiation and 2 Fold Contrast Dose Reduction Providing Basis for A Longitudinal Smoking Cessation Study



0.44 mSv

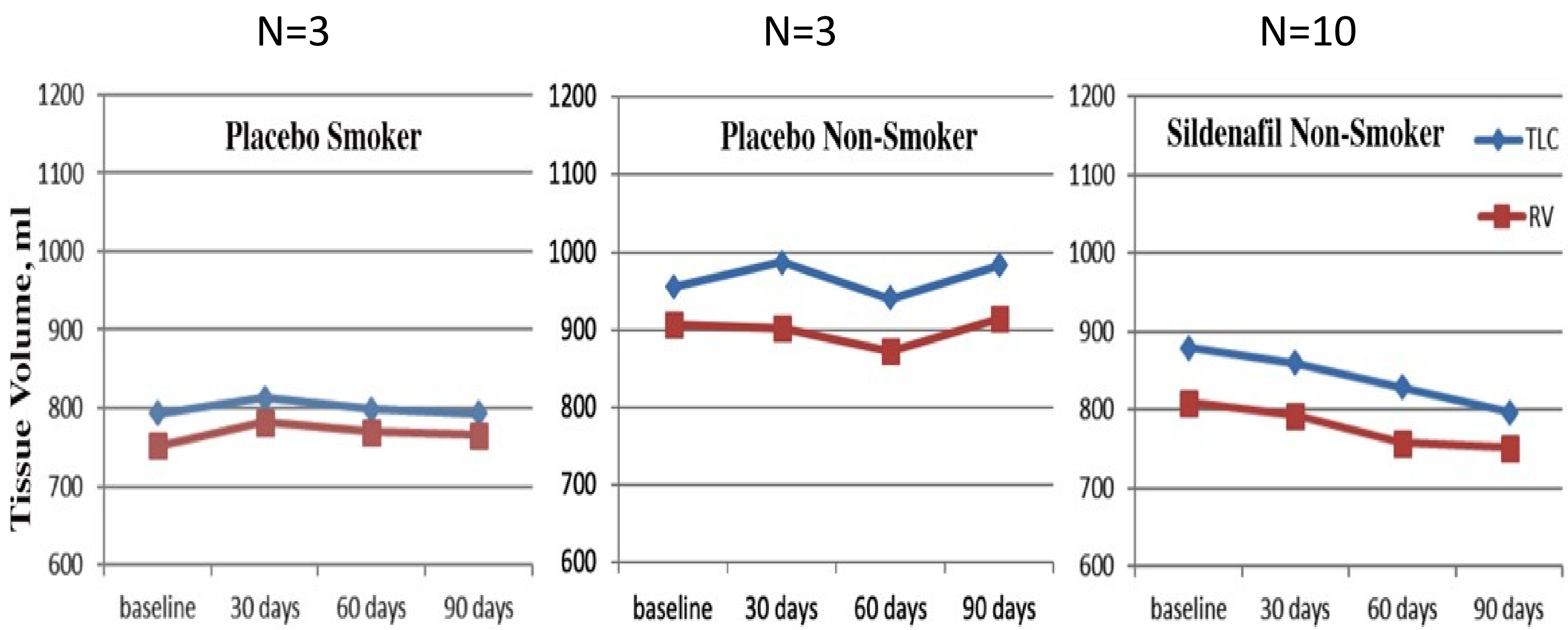
Inspiration - TLC	**SPIROMICS (OLD)**	**SPIROMICS II (Low-Dose)**	**Smoking Cessation**	**PBV - Flash (OLD)**	**PBV - Force**
Detector Config.	192 x 0.6mm	192 x 0.6mm	192 x 0.6mm	64 x 0.6mm	192 x 0.6mm
Rotation Time	0.5	0.25	0.5	0.285	0.25
kV	120	120	Sn100	80/Sn140	80/Sn150
mAs	110	36 (Reference mAs)	188 (Reference mAs)	291/124 (Reference mAs)	210/117 (Reference mAs)
CareDose	OFF	ON	ON	OFF	ON
CTDIvol	7.6mGy	2.4mGy	0.65mGy	11.38mGy	7.27mGy
Approx Dose for 30cm chest of average adult	3.2mSv	1.6mSv	0.44mSv	4.8mSv	3.05mSv
Contrast Dilution	NA	NA	NA	None	50% Isovue/ 50% Saline

*Flash Scanner PBV (old) contrast amount was determined with test bolus
*Total Contrast Solution Equation for the Force:
rate (delay time + scan time) +8cc (to ensure contrast is flowing during scan)
rate = 4cc/sec of half concentration Isovue 370
Delay = 17sec
Average total solution = ~86cc Average
amount of Isovue 370 - ~43cc.

Hammond E, et al. Med Phys. 2017 Sep;44(9):4747-4757.
Hammond E, et al. Med Phys. 2018 Jun 21.

90 Day Smoking Cessation with Sildenafil and Placebo

Lung issue volume changes
Preliminary Results



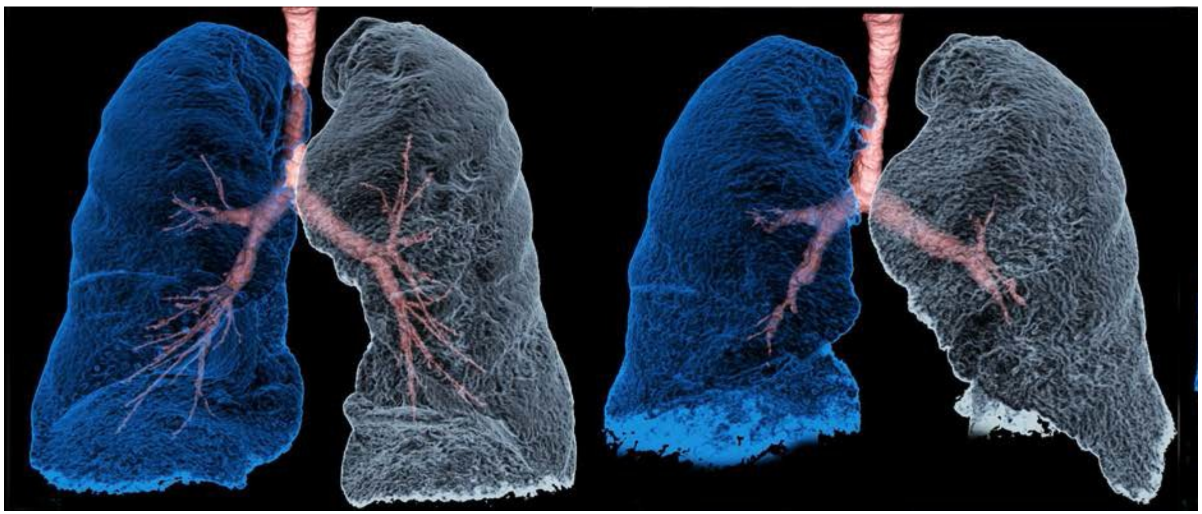
Lung tissue volume Δ for three subject groups assessed at both TLC and RV

Hoffman EA et al, Fleischner Society Meeting, Paris, 2019

Lung Volumes for Assessment of V/Q

V **Q**

Non-contrast (TLC) → PBV-Based Virtual Non-Contrast (FRC) / DECT PBV (FRC)

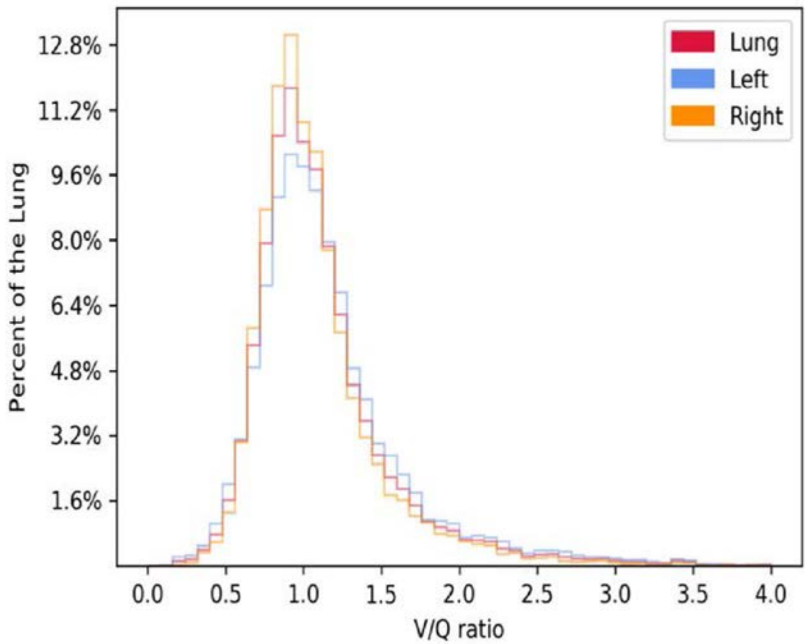


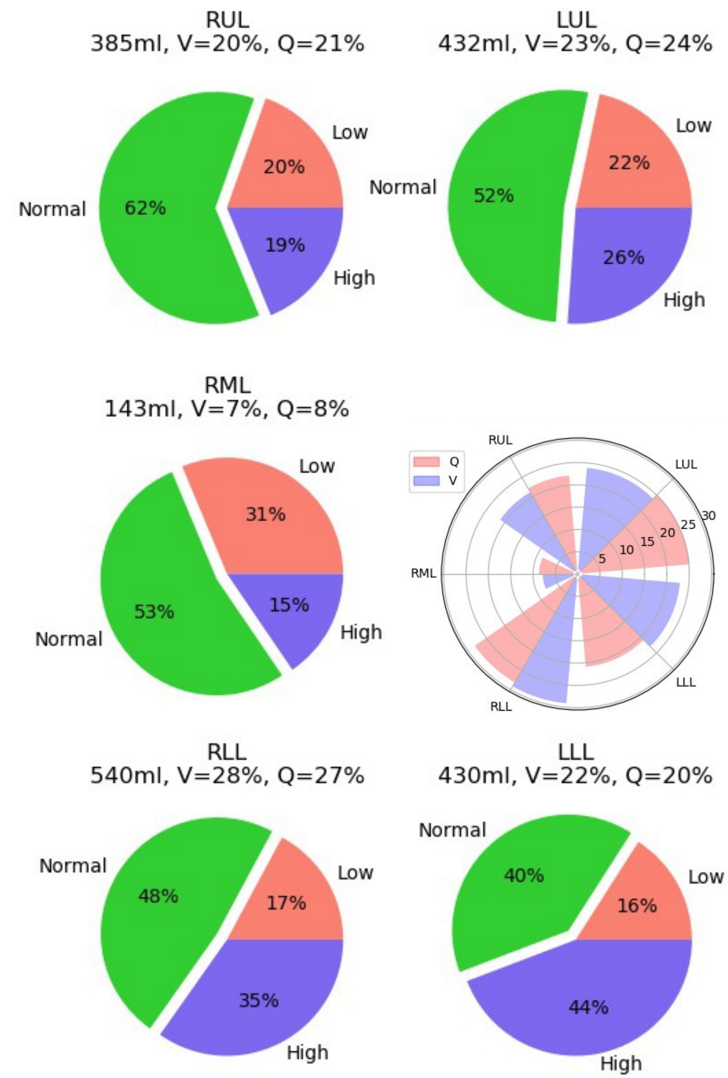
UNITS of V and Q in % of Total Ventilation or % of Total PBV

APPIL

Provisional Patent Filed: Univ of Iowa 2019

Lung and Lobar Distribution of V/Q:
High, Normal and Low





V/Q High:
>1.2
Normal: 0.8-1.2
Low: <0.8

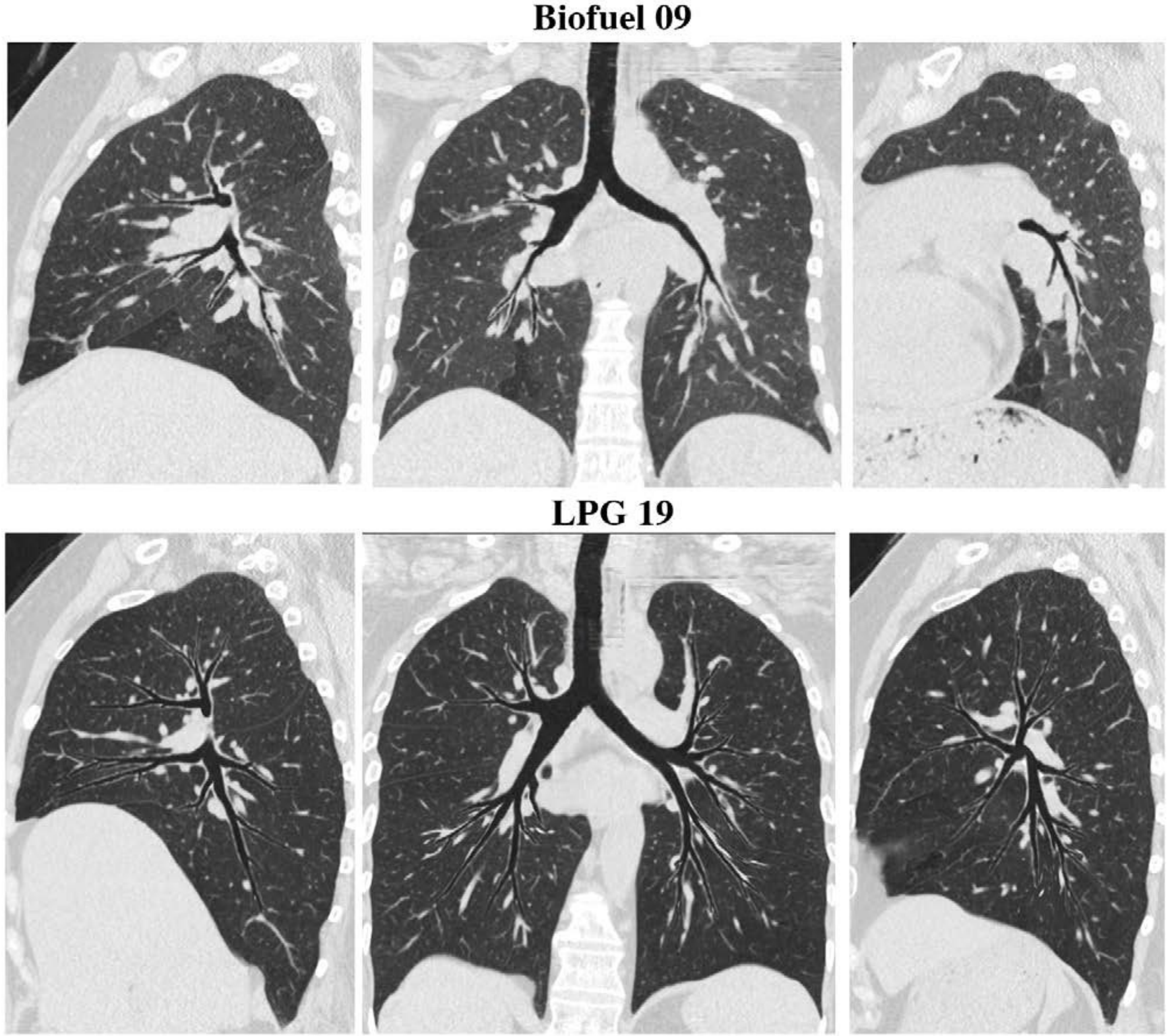
Assessment of the Lung via CT in Individuals Cooking Indoors with Solid Biofuels and Poor Ventilation

~3 billion people rely on solid biofuels for cooking and heating and this is the largest risk factor for COPD worldwide. -WHO

" [there is a] persistence of physiologic, radiographic, and histopathologic abnormalities years after removal from exposure" *Asaad A Respir Med Case Rep. 2017 Dec 24;23:74-76.*

Assessment of the Lung via CT in Individuals Cooking Indoors with Solid Biofuels and Poor Ventilation

Assessment of the Lung via CT in Individuals Cooking Indoors with Solid Biofuels and Poor Ventilation



Assessment of the Lung via CT in Individuals Cooking Indoors with Solid Biofuels and Poor Ventilation

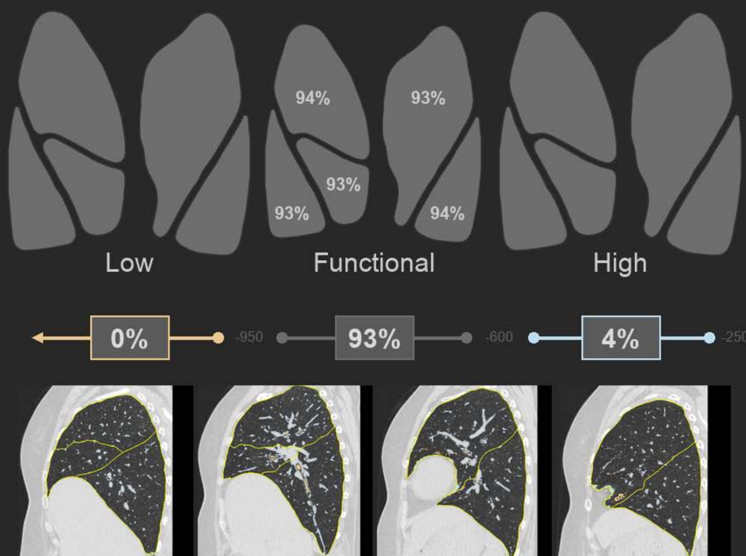
LPG

Not For Clinical Use

LungPrint

Discovery

Density



	Total	Right	Left	RUL	RML	RLL	LUL	LLL
Volume (L)	3.2	1.7	1.6	0.5	0.3	0.9	0.8	0.7
Low Density (%)	0	0	1	0	1	0	1	0
High Density (%)	4	4	4	4	4	4	4	4
Functional (%)	93	93	93	94	93	93	93	94

This report should not be used for primary diagnosis.

VIDA 2500 Crosspark Rd W250 BioVentures Center Coralville, IA 52241

www.vidalung.ai 1.855.900.8432

VIDA|vision version 2.1.0 (1)00852426007015(10)1D0D000C

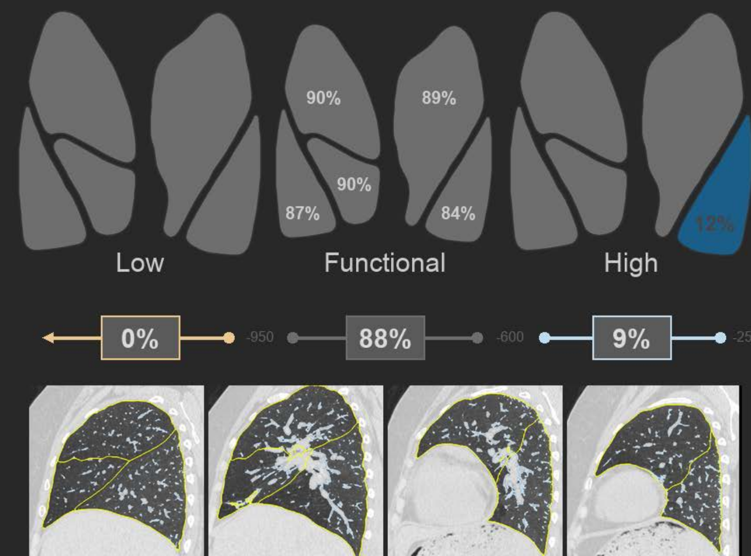
Biomass

Not For Clinical Use

LungPrint

Discovery

Density



	Total	Right	Left	RUL	RML	RLL	LUL	LLL
Volume (L)	2.0	1.1	0.8	0.4	0.2	0.5	0.4	0.4
Low Density (%)	0	0	0	0	0	0	0	0
High Density (%)	9	8	10	7	7	9	9	12
Functional (%)	88	89	86	90	90	87	89	84

This report should not be used for primary diagnosis.

VIDA 2500 Crosspark Rd W250 BioVentures Center Coralville, IA 52241

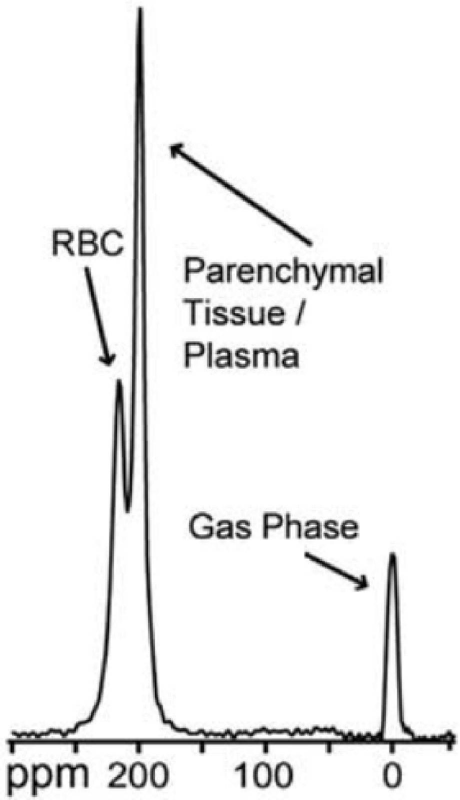
www.vidalung.ai 1.855.900.8432

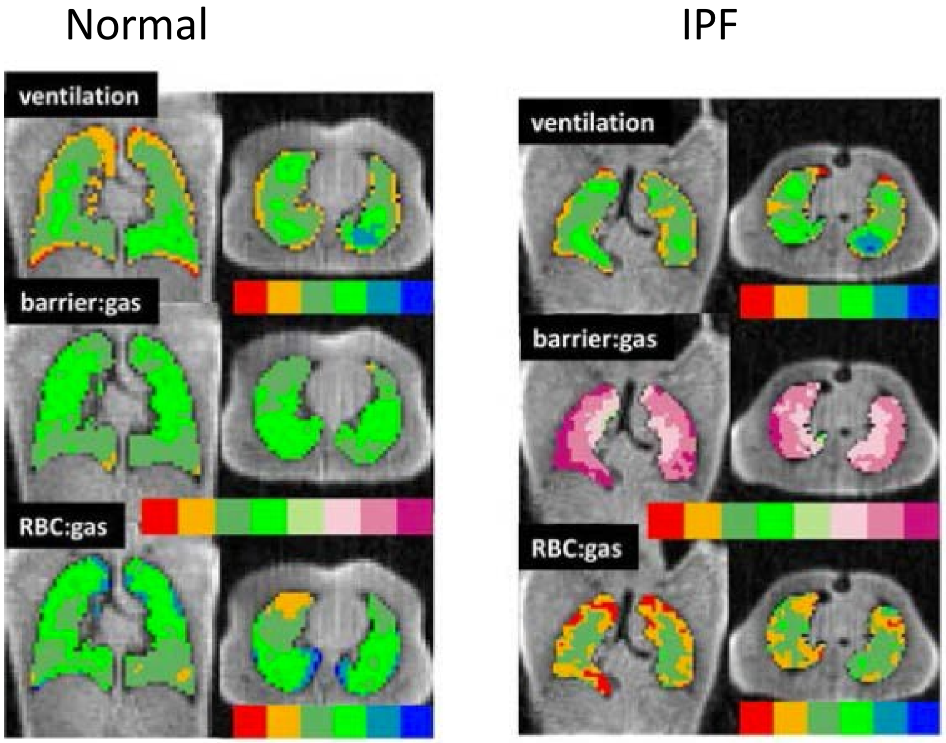
VIDA|vision version 2.1.0 (1)00852426007015(10)1D0D000C

PRM vs DPM
Threshold vs Integration of Regional Mechanics

	Biomass				LPG			
Lung Location	**PRM AT %**	**DPM AT %**	**Jacobian Mean**	**ADI Mean**	**PRM AT %**	**DPM AT %**	**Jacobian Mean**	**ADI Mean**
Both	2.6	55.7	1.18	0.19	2.8	18.2	1.80	0.34
Left	1.9	57.4	1.14	0.18	4.5	22.8	1.74	0.32
LLL	1.8	58.8	1.12	0.17	4.7	23.5	1.74	0.32
LUL	2.1	56.1	1.17	0.20	4.3	22.1	1.74	0.32
Right	3.2	54.4	1.21	0.20	1.1	13.7	1.86	0.35
RLL	1.9	49.9	1.20	0.17	0.6	12.8	1.85	0.35
RML	8.6	65.5	1.20	0.22	2.2	15.3	1.84	0.40
RUL	1.7	54.4	1.24	0.23	1.3	14.3	1.88	0.33

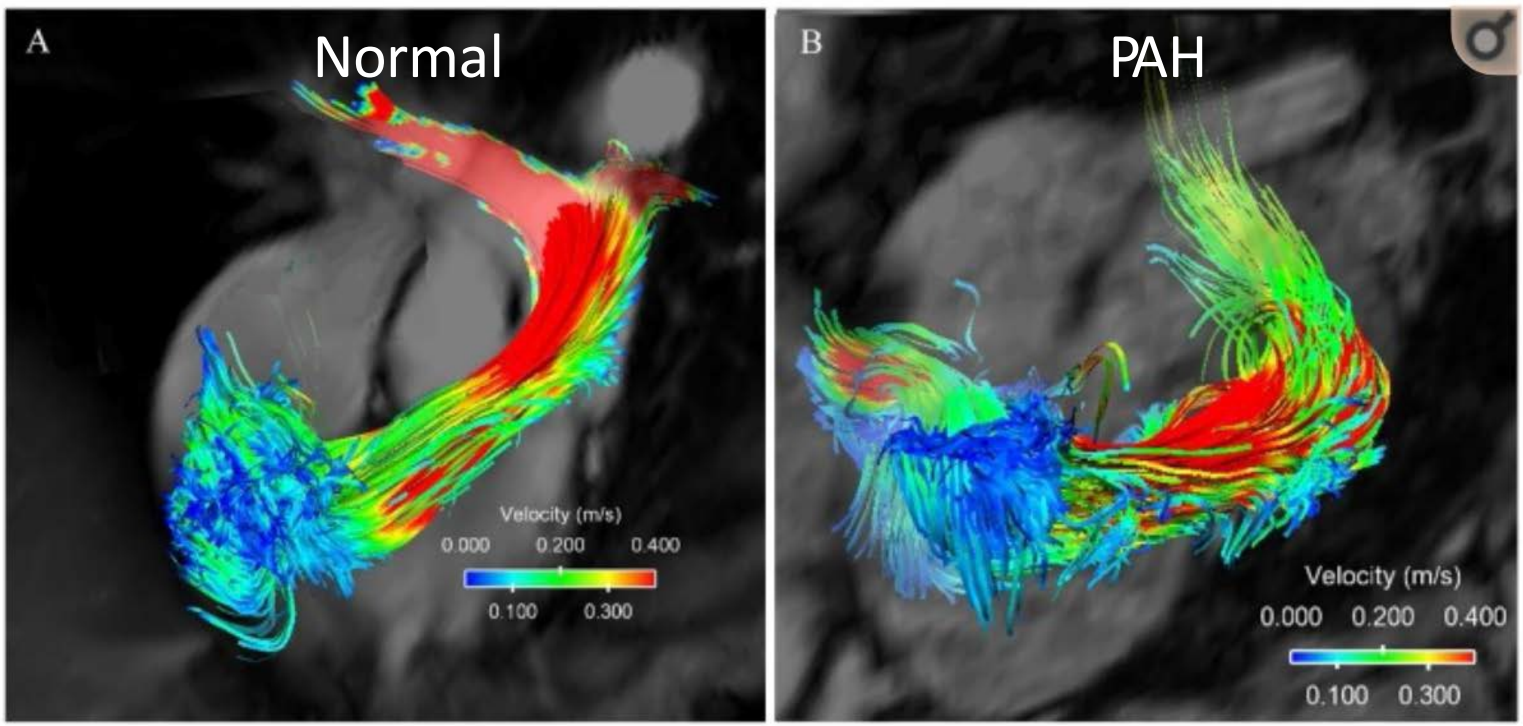
Hyperpolarized ^{129}Xe





Mammarappallil JG, Rankine L, Wild JM, Driehuys
J Thorac Imaging. 2019 Mar;34(2) 136-150. .

MRI 4D Flow As An Index of Increased Pulmonary Arterial Resistance



From: Han QJ et al: PLoS One 2015; Sept 29; 10 (9) :e0138365