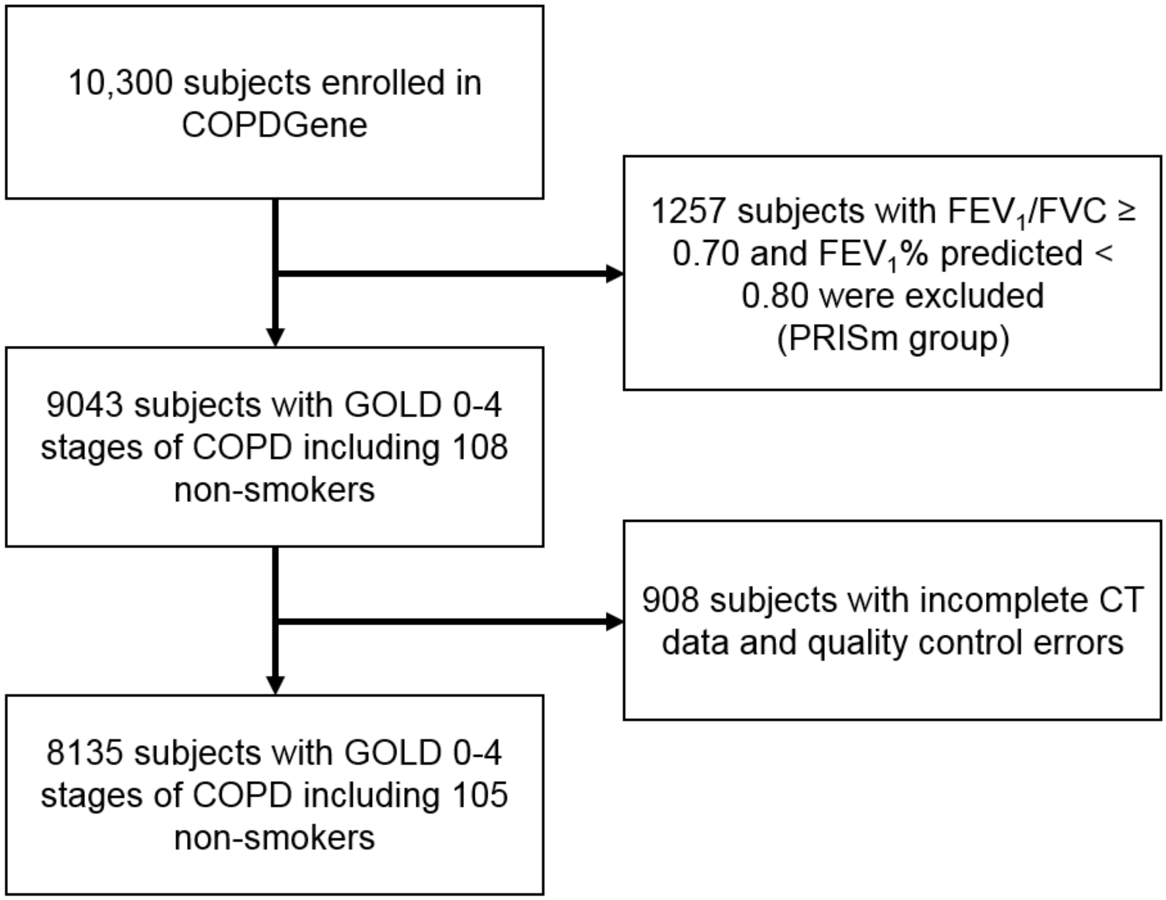
Supplemental Figure 1: Consort Diagram



Additional Results: Additional results displayed for AFD and peribronchial emphysema separately in Supplemental Tables 1, 2, 3 and 5

Supplemental Table 1: Multivariable Associations of Non-normalized CT parameters with Lung Function and Respiratory Morbidity*

	FEV_1 (L)		FEV1/FVC		6MWD (ft)		SGRQ	
	β (95%CI)	p-value	β (95%CI)	p-value	β (95%CI)	p-value	β (95%CI)	p-value
CT Emphysema(%)	-0.04 (-0.05, -0.04)	< 0.001	-0.01 (-0.011, -0.010)	< 0.001	-15.20 (-16.06,-14.33)	< 0.001	1.05 (1.00,1.10)	< 0.001
CT Peribronchial Emphysema (%)	-0.117 (-0.12,-0.11)	< 0.001	-0.03 (-0.031,-0.030)	< 0.001	-34.04 (-36.98,-31.10)	< 0.001	2.63 (2.46,2.79)	< 0.001
Pi10	-2.51 (-2.64,-2.39)	< 0.001	-0.34 (-0.36,-0.31)	< 0.001	-745.44 (-808.37,-682.50)	< 0.001	51.41 (47.75,55.05)	< 0.001
Airway Fractal Dimension (AFD)	3.73 (3.56,3.90)	< 0.001	0.66 (0.63,0.70)	< 0.001	1060.70 (971.40,1150.01)	< 0.001	-70.44 (-75.67,-65.20)	< 0.001
CT Gas Trapping (%)	-0.02 (-0.03,-0.02)	< 0.001	-0.006 (-0.006,-0.006)	< 0.001	-8.63 (-9.08, -8.18)	< 0.001	0.62 (0.60,0.65)	< 0.001

β = Regression co-efficient. CI = Confidence Interval.

FEV_1 = Forced expiratory volume in the first second. FVC = Forced vital capacity. 6MWD = 6-Minute Walk Distance. 6MWD = 6-Minute Walk Distance. SGRQ = St. George’s Respiratory Questionnaire. CT = Computed Tomography. Pi10 = Square root of the wall area of a hypothetical airway with a lumen perimeter of 10mm

*All models adjusted for age, race, gender, smoking status, pack years, body mass index, CT scanner type.

Supplemental Table 2: Multivariable Associations of Normalized CT parameters with Lung Function and Respiratory Morbidity*

	FEV_1 (L)		FEV1/FVC		6MWD (ft)		SGRQ	
	β (95%CI)	**p-value**	**β (95%CI)**	**p-value**	**β (95%CI)**	**p-value**	**β (95%CI)**	**p-value**
CT Emphysema (%)	-0.49 (-0.50, -0.47)	< 0.001	-1.15 (-0.11,-0.11)	< 0.001	-153.91 (-162.67, -145.12)	< 0.001	10.71 (10.22, 11.20)	< 0.001
CT Peribronchial Emphysema	-0.37 (-0.38, -0.35)	< 0.001	-0.09 (-0.10, -0.09)	< 0.001	-107.23 (-116.50 , -97.96)	< 0.001	8.28 (7.75, 8.81)	< 0.001
Pi10	-0.32 (-0.34, -0.31)	< 0.001	-0.04 (-0.04,-0.04)	< 0.001	-97.44 (-105.67, -89.22)	< 0.001	6.71 (6.24, 7.19)	< 0.001
Airway Fractal Dimension (AFD)	0.34 (0.33, 0.36)	< 0.001	0.06 (0.05, 0.06)	< 0.001	98.26 (89.99, 106.53)	< 0.001	-6.52 (-7.01, -6.04)	< 0.001
CT Gas Trapping (%)	-0.60 (-0.62, -0.59)	< 0.001	-0.13 (-0.13, -0.13)	< 0.001	-177.21 (-186.41, -168.01)	< 0.001	12.90 (12.39, 13.40)	< 0.001

β = Regression co-efficient. CI = Confidence Interval.

FEV_1 = Forced expiratory volume in the first second. FVC = Forced vital capacity. 6MWD = 6-Minute Walk Distance. 6MWD = 6-Minute Walk Distance. SGRQ = St. George's Respiratory Questionnaire. CT = Computed Tomography. Pi10 = Square root of the wall area of a hypothetical airway with a lumen perimeter of 10mm

*All models adjusted for age, race, gender, smoking status, pack years, body mass index, CT scanner type.

To enable comparisons between the various radiological parameters and their associations with outcomes, we "normalized" the CT parameters by scaling and centering them by (value-mean)/SD.

Supplemental Table 3: Multivariable Associations of Radiological Parameters with FEV_1 change (ml/year)

	Non-normalized		Normalized	
	β (95%CI)	**p-value**	**β (95%CI)**	**p-value**
CT Emphysema (%)	0.86 (0.60,1.11)	< 0.001	7.55 (5.34, 9.76)	< 0.001
CT Peribronchial Emphysema (%)	2.06 (1.37,2.75)	< 0.001	6.31 (4.21, 8.42)	< 0.001
Pi10	-12.82 (-28.31,2.66)	0.104	-1.57 (-3.48, 0.32)	0.105
Airway Fractal Dimension (AFD)	-26.42 (-47.66,-5.17)	0.014	-2.51 (-4.53, -0.49)	0.014
CT Gas Trapping (%)	0.65 (0.52,0.79)	< 0.001	12.23 (9.67, 14.79)	< 0.001

β = Regression co-efficient. CI = Confidence Interval.

FEV_1 = Forced expiratory volume in the first second. Pi10 = Square root of the wall area of a hypothetical airway with a lumen perimeter of 10mm

*All models adjusted for age, race, gender, smoking status, pack years, body mass index, CT scanner type, and FEV1 at baseline.

To enable comparisons between the various radiological parameters and their associations with outcomes, we “normalized” the CT parameters by scaling and centering them by (value-mean)/SD.

Supplemental Table 4: Univariate and multivariate regression with FEV_1 (L)

	Univariate Regression		**Multivariate Regression***	
Parameter	**β (95%CI)**	**p-value**	**β (95%CI)**	**p-value**
Age (years)	-0.04 (-0.04, -0.04)	< 0.001	-0.02 (-0.02, -0.02)	< 0.001
Race, African American	0.14 (0.09, 0.18)	<0.001	-0.17 (-0.20, -0.14)	< 0.001
Sex, female	-0.68 (-0.72, -0.64)	< 0.001	-0.68 (-0.70, -0.65)	< 0.001
Body Mass Index (kg/m2)	-12.94 (-14.31, -11.57)	< 0.001	-0.01 (-0.01, -0.001)	< 0.001
Smoking Pack Years	-0.009 (-0.009, -0.008)	< 0.001	-0.002 (-0.003, -0.002)	< 0.001
Smoking Status, Current	0.44 (0.40,0.48)	< 0.001	-0.04 (-0.07, -0.01)	< 0.001
Percent CT Emphysema	-0.05 (-0.05, -0.04)	< 0.001	-0.01 (-0.01, -0.01)	< 0.001
Percent CT Gas Trapping	-0.02 (-0.03, -0.02)	< 0.001	-0.01 (-0.01, -0.01)	< 0.001
Pi10	-3.01 (-3.16, -2.87)	< 0.001	-1.71 (-1.80, -1.61)	< 0.001
AFD	3.71 (3.50, 3.92)	< 0.001	1.62 (1.48, 1.76)	< 0.001

Adjusted R^2: 0.726

β = Regression co-efficient. CI = Confidence Interval.

FEV_1 = Forced expiratory volume in the first second. CT = Computed tomography. Pi10 = Square root of the wall area of a hypothetical airway with a lumen perimeter of 10mm. AFD = Airway Fractal Dimension.

*All models adjusted for CT scanner type.

Supplemental Table 5: Multivariable associations of peribronchial emphysema (%) and airway fractal dimension (AFD) with lung function and respiratory morbidity*

	Peribronchial Emphysema (%)		Airway Fractal Dimension (AFD)	
	β (95%CI)	**p-value**	**β (95%CI)**	**p-value**
FEV_1 (L)	-0.12 (-0.13, -0.12)	< 0.001	3.08 (2.92, 3.25)	< 0.001
FEV_1/FVC	-0.032 (-0.031, -0.030)	< 0.001	0.58 (0.55, 0.61)	< 0.001
Six-minute walk distance (ft)	-36.19 (-39.05, -33.34)	< 0.001	855.63 (765.50, 945.87)	< 0.001
SGRQ	2.79 (2.63, 2.95)	< 0.001	-55.60 (-60.84, -50.36)	< 0.001
Change in FEV_1 after 5-year follow up ‡	2.17 (1.47, 2.87)	< 0.001	-28.98 (-49.92, -8.04)	0.006

β = Regression co-efficient. CI = Confidence Interval.

FEV_1 = Forced expiratory volume in the first second. FVC = Forced vital capacity. SGRQ = St. George's Respiratory Questionnaire.

*adjusted for age, race, sex, smoking status, pack years, body mass index, CT scanner type, and Pi10. CT emphysema (%) was excluded from the models to avoid collinearity and from the airway fractal dimension (AFD) model to aid comparisons of the two models.

‡ adjusted for age, race, gender, smoking status, pack years, body mass index, FEV_1 at baseline, CT scanner type, and Pi10 (Square root of the wall area of a hypothetical airway with a lumen perimeter of 10mm). Change in FEV_1 expressed in ml/year.

Airway Fractal Dimension, Peribronchial Emphysema and Survival:

In separate models, we also compared the relative independent value of peribronchial emphysema and AFD in predicting mortality in subjects with COPD, with adjustment for age, race, sex, BMI, and pack-years of smoking. Both peribronchial emphysema (adjusted HR=1.07, 1.06 to 1.09, p<0.001) and AFD (adjusted HR=0.04, 0.02 to 0.10, p<0.001) were associated with mortality. In combined models that included both peribronchial emphysema and Pi10, AFD remained significantly associated with mortality (adjusted HR=0.15, 0.07 to 0.32, p<0.001). For these models, we did not adjust for CT emphysema as a covariate as peribronchial emphysema is a part of overall emphysema.

Methods:

<u>Airway Fractal Dimension</u>:

Fractal patterns have been observed in several naturally occurring phenomenon, including branching tree structures such as the human airway tree. The branching patterns of an airway tree are complex and self-repetitive, and do not adhere to regular Euclidean geometry explained through integer dimensions (D = 1, 2, 3). Such self-similar structures are better represented in fractal (or Fractional) dimensions (FD = 1.2, 2.8, 3.2). Fractal dimensions were originally defined by Mandelbrot, providing a simplified estimate of the complexity and self-similarity of objects in nature that follow fractal patterns.[1] Fractal dimensions have been previously used to describe the geometrical properties of an airway tree through digitized airway casts and also used to quantify the space filling capacity of emphysematous regions in the lung.[2-4]

Measurements of traditional geometric shapes scale predictably in relation to the topological space which they occupy and are related by the inverse power law. Scaling the size of an N dimensional object by a factor of s will increase the measurement of its N dimensional metric by a factor of N^s. For example, scaling the side length of a cube by a factor of 2 will increase its volume by a factor of $2^3 = 8$. Therefore, the number of measuring blocks *N(s)* required to estimate the volume of a geometric shape will be related to both the dimension *(D)* of the object and the size *(s)* of the measuring block. This scaling relationship is defined by the general equation[4]:

$$N(s) \propto 1/_{s^D}$$

$$D = \lim_{s \to 0} \left(\log N(s) \Big/ \log\left(1/_{s}\right) \right)$$

$$D = -\frac{d(\log(N(s)))}{d(\log(s))}$$

By repeated measurements of N(s) at different levels of scale (s), an estimate of the dimension of the fractal pattern can be estimated. This is the basis of the Minkowski-Bouligand dimension, also known as the box-counting dimension (**Supplemental Figure 2**). For simple geometric shapes, this will also equal their topological dimension.

A simple algorithm was implemented in MATLAB to estimate the box-counting dimension as follows: (https://www.mathworks.com/matlabcentral/fileexchange/13063-boxcount?focused=5083247&tab=example)

1. A binary segmentation image representation of the airway tree was generated using Pulmonary Workstation software (VIDA Diagnostics, Coralville, IA).

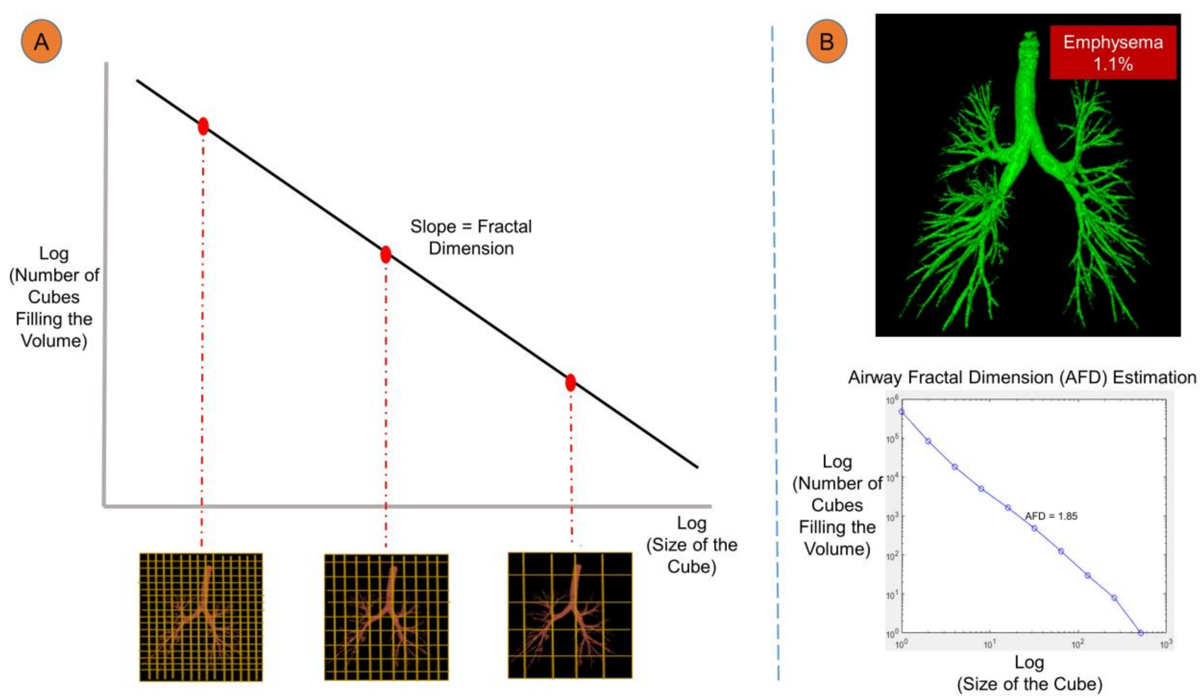
2. The image was padded with zeroes to generate a cube whose side equals the smallest power of two that contains the image. For instance, an image of size 500x500x300 is padded to 512x512x512.

3. The number of voxels that contained the segmented airway tree was counted. This corresponds to *N (1)*, i.e. count of grids at grid size $s = 1$.

4. Progressively larger grids were overlaid on the segmentation image, increasing the side of the grid by a factor of 2 at each step. The number of grids that contain any part of the segmented airway tree was counted to estimate *N(s) at s = 2, 4, 8… up to maximum of image size (512 in the example).*

5. Log *(N(s))* and *log(s)* were estimated. The first order derivative of both terms was approximated using the difference between consecutive terms in the respective sequences.

6. The dimension *D* was estimated at each value of *s* as the ratio of the derivatives as per Equation (3). The average value of *D* (over the most stable range) was used as the estimate of the fractal dimension of the airway tree under study.

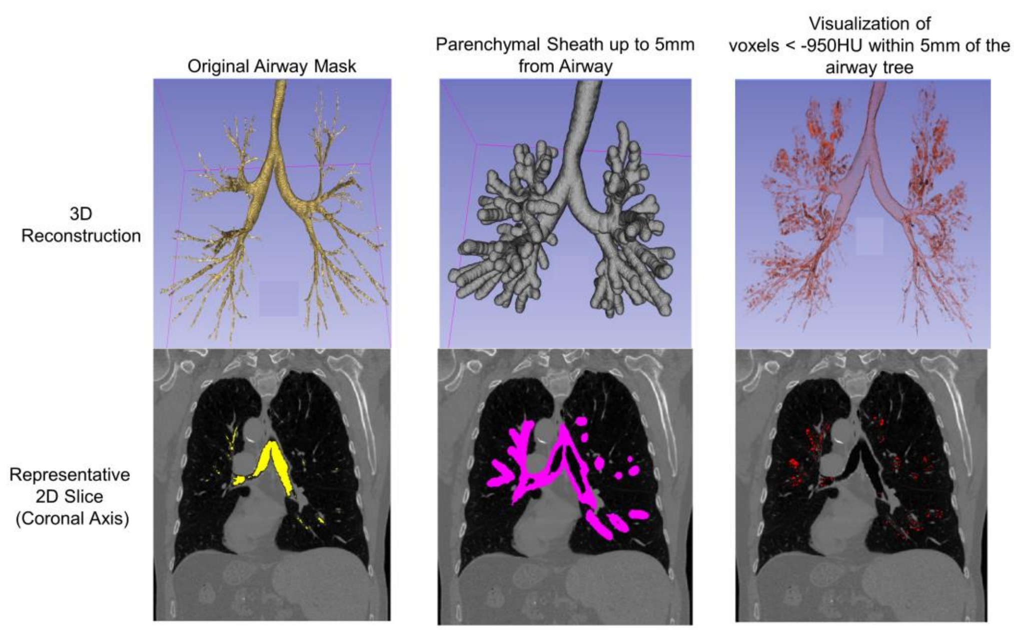


Supplemental Figure 2: Estimation of airway fractal dimension (AFD). **(A)** The Kolmogorov box-counting method was adapted to 3-dimensional CT reconstruction of an airway tree (cube-counting). The segmented airway tree was converted to a binary image for processing. Cubes of progressively increasing side length "s" (initial value s = 1; increasing in powers of 2 to a maximum of the image size) were iteratively overlaid over the binary airway mask and the number of cubes 'N' containing the airway were identified at each iteration. The number of cubes required to cover the airway is related to the size of the cube by an inverse power law. The slope of the least-squares best-fit regression line between the log (N) and log (1/s) was computed to derive the AFD. **(B)** The AFD of a representative subject without airflow obstruction in the COPDGene cohort. The greater the complexity of how the branches fill up space, the greater is the AFD.

The current method does not incorporate offsets or angular orientation changes to estimate the minimum number of grids required at each stage. This improves computational efficiency of the algorithm at the expense of bias towards lower estimates of fractal dimension. However, smaller scale grids are less susceptible to these bias conditions. Since the average value is computed over the most stable values of *D*, and these are at the lower scale ranges, the fractal dimension estimates used here are considered reliable for the purposes of our study.

<u>Estimation of Peribronchial Emphysema (%)</u>:

To quantify the emphysematous voxels within 5mm of airway tree, a distance map of the binary airway mask was initially created where the value at a particular location in the lung represents its nearest distance to the airway tree. Another binary mask was created with the voxels within 5mm distance of the airway tree, creating a parenchymal sheath around the airways (**Supplemental Figure 3**). The percentage of emphysema (voxels <-950HU) was then estimated within the parenchymal sheath, representing %peribronchial emphysema.



Supplemental Figure 3: Estimation of Peribronchial Emphysema. A parenchymal sheath of 5mm was created around the original airway mask (binary) and peribronchial emphysema was computed by the percentage of emphysematous voxels (<-950HU) within 5mm of the airway.

IRB Approval:
The COPDGene Study was approved by the Institutional Review Boards of all 21 participating clinical centers. Ann Arbor VA Medical Center 2014-060462 (Ann Arbor VA IRB); Baylor College of Medicine H-22209 (IRB for Baylor College of Medicine); Brigham and Women's Hospital 2007P000554 (Partners Human Research Committee); Columbia Univ. Medical Center AAAC9324 (Columbia University IRB); Duke Univ. Medical Center Pro00004464 (Duke University Health System IRB); Johns Hopkins University NA_00011524 (Johns Hopkins Medicine IRB); L.A. Biomedical Research Inst. 12756-03 (John F. Wolf, M.D. Human Subjects Committee); Michael E. DeBakey VAMC H-22202 (Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals); Minneapolis VA Medical Center 4128-A (Minneapolis VA Health Care System Minnesota); Health Partners Twin Cities 07-127 (Health Partners IRB); Morehouse School of Medicine 97826 (Morehouse School of Medicine IRB); National Jewish Health 1883a (National Jewish Health IRB); Reliant Medical Group (Fallon) 1441 (Reliant Medical Group IRB); Temple University 21659 (Temple IRB); Univ. of Alabama, Birmingham F070712014 (University of Alabama at Birmingham IRB for Human Use); Univ. of California, San Diego 140070 (UCSD Human Research Protections Program); University of Iowa 200710717 (University of Iowa IRB); University of Michigan HUM00014973 (University of Michigan Medical School IRB); University of Minnesota 0801M24949 (University of Minnesota IRB Human Subjects Committee); University of Pittsburgh #07120059 (University of Pittsburgh IRB); and UTHSC at San Antonio HSC20070644H (UT Health Science Center San Antonio IRB)

References:

1. Mandelbrot BB, Pignoni R. *The fractal geometry of nature.* Vol 173: WH freeman New York; 1983.
2. Boser SR, Park H, Perry SF, Ménache MG, Green FH. Fractal geometry of airway remodeling in human asthma. *American journal of respiratory and critical care medicine.* 2005;172(7):817-823.
3. Mishima M, Hirai T, Itoh H, et al. Complexity of terminal airspace geometry assessed by lung computed tomography in normal subjects and patients with chronic obstructive pulmonary disease. *Proceedings of the National Academy of Sciences.* 1999;96(16):8829-8834.
4. Weibel ER. Fractal geometry: a design principle for living organisms. *American Journal of Physiology-Lung Cellular and Molecular Physiology.* 1991;261(6):L361-L369.