순환기의공학회, 부산 벡스코, 2018/6/23

멀티스케일 이미지 변수를 통한 천식과 만성기관지 호흡 장애 환자의 변이에 대한 비교분석

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ICFM

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PRESENTATION OVERVIEW

- **Predictive Framework with Asthma Imaging Data**
  - Functional Characteristics via Image Registration
  - Functional Characteristics via CT Density-based Air-trapping
  - Airway Structural Characteristics via Image Segmentation
  - Machine Learning-based Clustering Analysis
- **Applications of Multiscale QCT imaging-based metrics**

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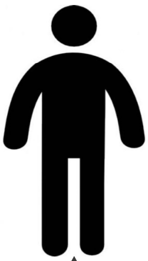
Predictive Framework with Asthma Imaging Data

AN EXAMPLE OF PREDICTIVE MODELING

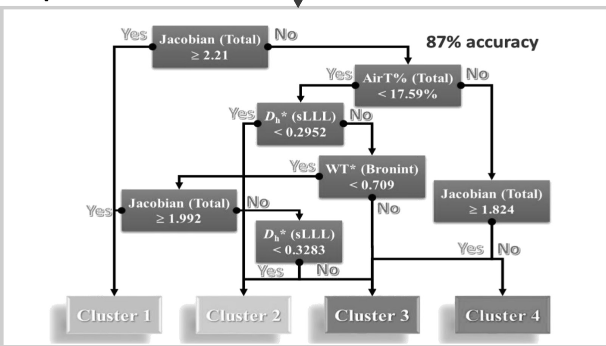
- QCT imaging at TLC and FRC
- Post processed imaging metrics

TLC: Inspiration scan
FRC: Expiration scan

Individual scale

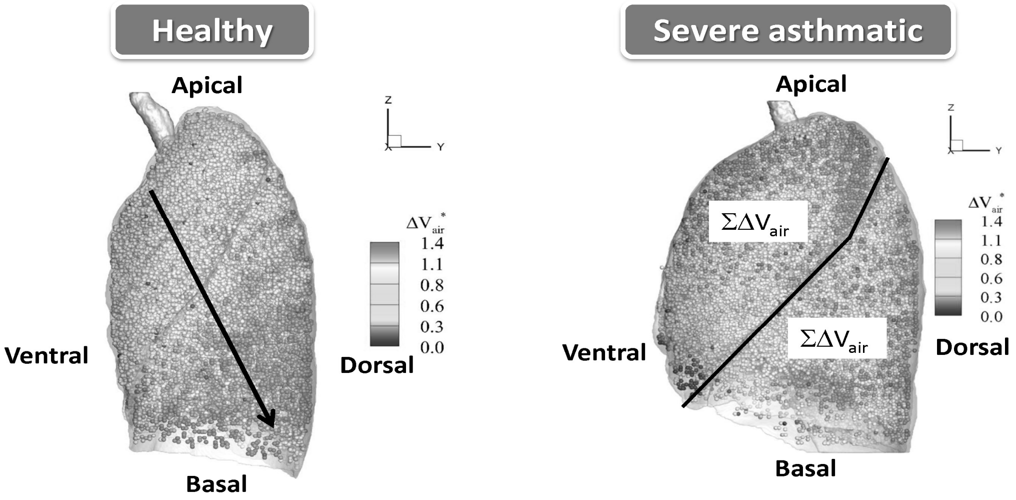


Population scale



- Predict clinical characteristics
- Predict CFD-based phenotypes

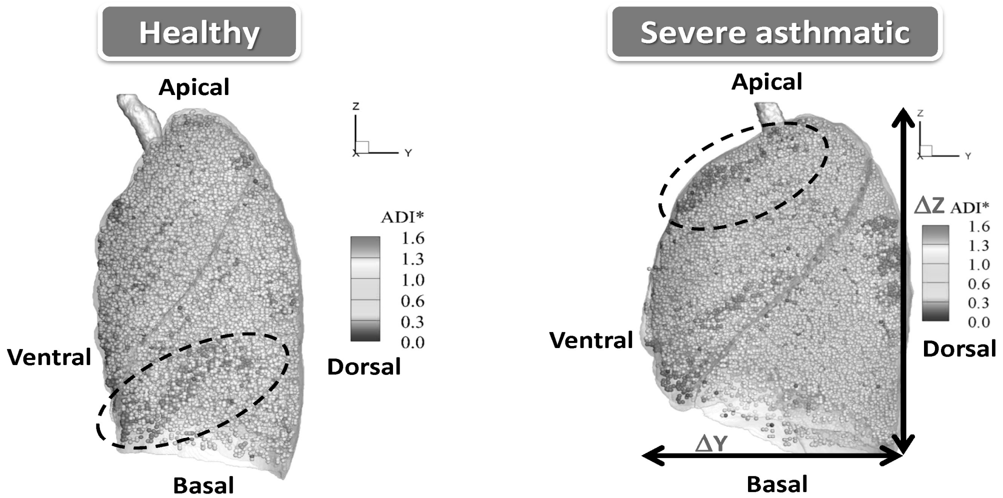
REGIONAL AIR VOLUME CHANGE ΔV_{air}



✓ **U/(M+L)|v** = the ratio of ΔV_{air} in upper lobes (LUL, RUL) to ΔV_{air} in middle and lower lobes (RML, LLL, RLL)

INTERDISCIPLINARY COMPUTATIONAL FLUID MECHANICS LABORATORY

ANISOTROPIC DEFORMATION INDEX (ADI)

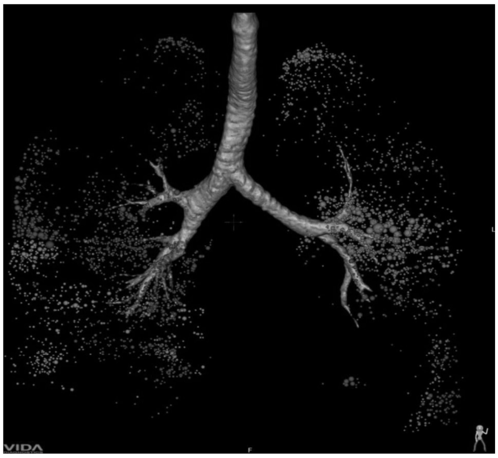


✓ **Lung shape** = the ratio of ΔZ to ΔY

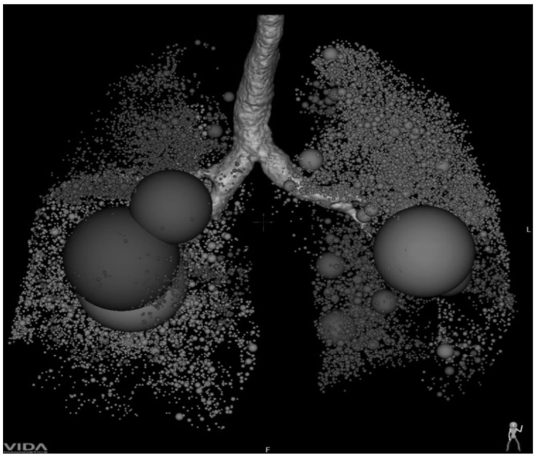
S Choi et al. (2013) *J Appl Physiol*, Registration-based assessment of regional lung function…

AIR-TRAPPING PERCENTAGE (AirT%)

Healthy

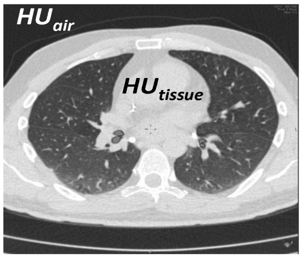


Severe asthmatic



INTERSITE PROTOCOL DIFFERENCE

- CT images from **two different centers**
  - **PITT**: The University of Pittsburgh (14 HS, 26 NSA and 30 SA)
  - **WSL**: Washington University in Saint Louis (11 HS, 16 NSA and 22 SA)



Imaging Centers	Scanners
PITT	General Electronics VCT 64
WSL	Siemens Sensation 16

HS: Healthy subjects
NSA: Non-severe asthmatics
SA: Severe asthmatics

CT Densities of HU_{air} and HU_{tissue} are different!

***Hounsfield Unit (HU)**

FRACTION-BASED AIR-TRAPPING

- **Air-fraction (β_{air})** is less sensitive to the **scanner difference** because it is a **non-dimensional** value, **unlike CT density.**

$$\beta_{air} = \frac{HU_{tissue} - I}{HU_{tissue} - HU_{air}}$$

$$I = \beta_{air} HU_{air,trachea} + \left(1 - \beta_{air}\right) HU_{tissue}$$

- Example (β_{air} =90%)

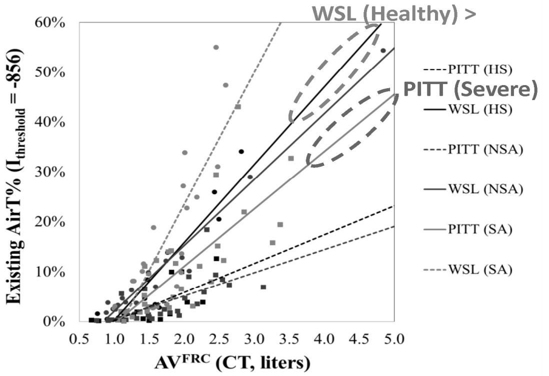
New approach | vs. | Existing approach

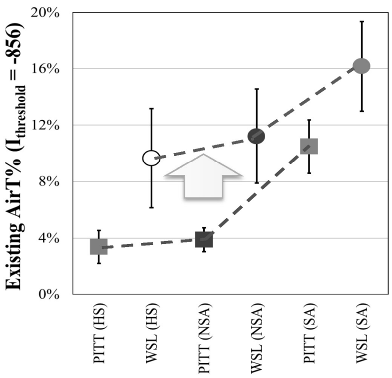
$$I_{threshold} = 0.9 HU_{air,trachea} + 0.1 HU_{tissue}$$ vs. $$I_{threshold} = -856\ HU$$

- HU_{air} was only corrected, because the difference of HU_{tissue} was marginal when obtaining the adjusted threshold.

EXISTING DENSITY-BASED AIR-TRAPPING

- **FRC (CT) volume vs. existing AirT% in three populations**

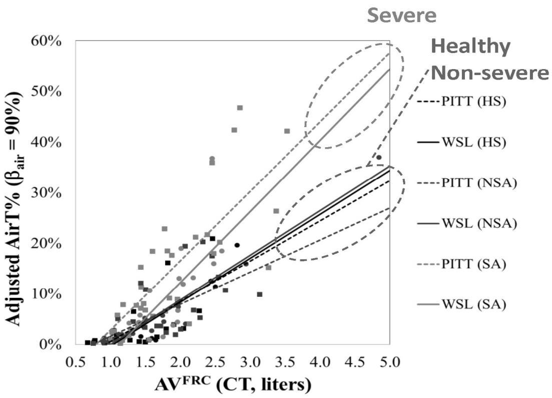


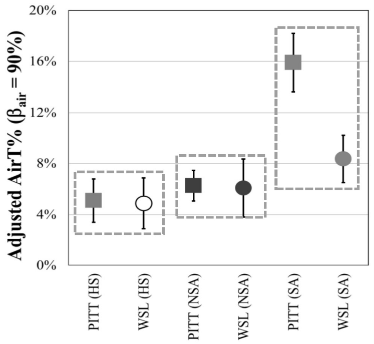


- There is **no consistency within groups** if existing AirT% is applied.
- **The slope of WSL HS is even steeper than PITT SA.**
- Overall AirT% of WSL **is much greater than** AirT% of PITT.

NEW FRACTION-BASED AIR-TRAPPING

➢ **FRC (CT) volume vs. Adjusted AirT% in three populations**





- After applying β_{air} of 90%, **each group has distinct slopes**.
- PITT (SA) has **lower FEV1/FVC** than WSL (SA) (P<0.05).

S Choi et al. (2014) *J Appl Physiol*, Improved CT-based Estimate of Pulmonary Gas-trapping…

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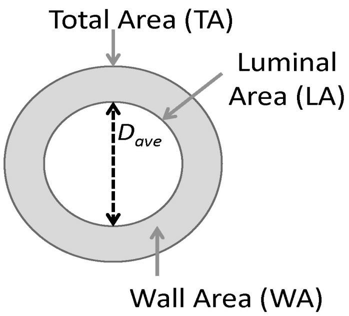
EXISTING BRONCHIAL VARIABLES



Luminal narrowing

- LA
- $D_{ave} = \sqrt{4LA/\pi}$

Wall thickening

- $WA\% = WA/TA$
- $WA = TA - LA$
- $WT = D_{outer} - D_{ave}$

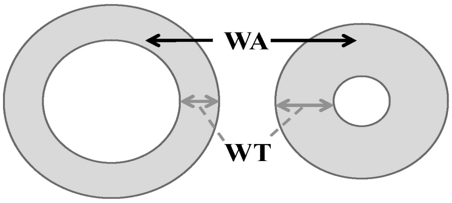
➢ Luminal narrowing is evaluated by **LA or D_{ave}**, whereas caution needs to be taken using **WA%, WA and WT** for wall thickening.

EXISTING BRONCHIAL VARIABLES

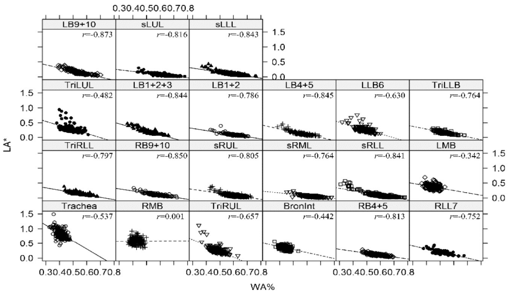
Wall thickening

- $WA\% = WA/TA$
- $WA = TA - LA$
- $WT = D_{outer} - D_{ave}$

➢ WA vs. WT



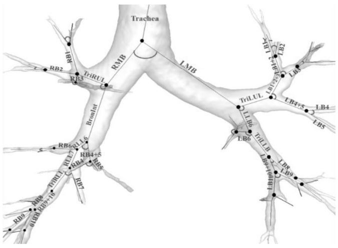
➢ WA% vs. LA*

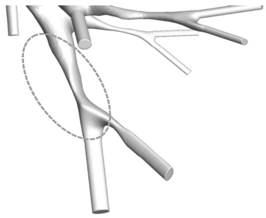


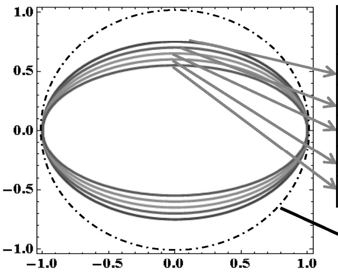
➢ Using **WT** would be the best way to assess wall thickening.

NEW BRONCHIAL STRUCTURAL VARIABLES

➢ **Bifurcation angle (*θ*), Circularity (*Cr*) and Hydraulic diameter (*D*$_h$))**







Cr	major axis / minor axis
0.985	1.333
0.977	1.429
0.966	1.538
0.953	1.667
0.937	1.818

$$\theta = \cos^{-1}\left(\frac{\mathbf{d}_1 \cdot \mathbf{d}_2}{|\mathbf{d}_1||\mathbf{d}_2|}\right)$$

$$Cr = \frac{\pi D_{ave}}{P_e}$$

$$D_h = \frac{4 \times LA}{P_e} = \frac{Cr^2}{\pi} P_e$$

NEW NORMALIZATION SCHEMES

Existing airway size assessments

Airway narrowing:
LA/**BSA** (Luminal area / Body surface area)

Wall thickening:
WA/**BSA** (Wall area / Body surface area)

✓ **BSA** ~ function (**Height**, **Weight**)

New airway size assessments*

Prediction of tracheal diameter and wall thickness from 61 healthy subjects

$D_{trachea,pred}$ **(mm)** = 16.446 – 2.4019 gender – 0.29881 gender×age + 0.02848 age×height + 0.17866 gender×age×height

$WT_{trachea,pred}$ **(mm)** = 4.5493 – 0.5007 gender + 0.3007 $\log_{10}$(age) × height

✓ Gender is an important variable of airway size.

	$BSA^{1/2}$	$D_{trachea,pred}$	Correlation Compare (*P*)
$D_{trachea}$	R = 0.48	**R = 0.79**	< 0.001
D_{LMB}	R = 0.45	**R = 0.68**	< 0.05
D_{RMB}	R = 0.43	**R = 0.71**	< 0.01

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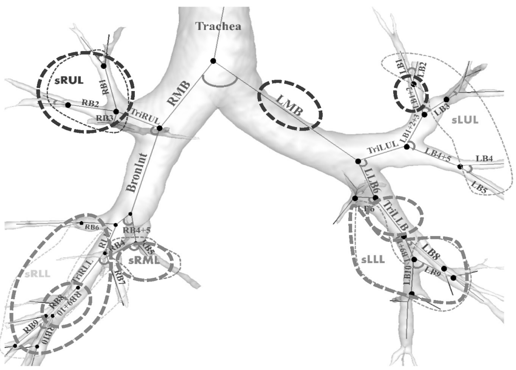
WALL THICKNESS & HYDRAULIC DIAMETER

Normalized wall thickness (WT*)

	Healthy subjects	Non-severe asthmatics	Severe asthmatics	Kruskal-Wallis tests (P value)
sRUL	0.612 (0.05)	0.608 (0.04)	0.630 (0.05)	< 0.005 †‡
LMB	0.748 (0.09)	0.773 (0.09)	0.794 (0.09)	< 0.005 ‡
LB1+2	0.631 (0.06)	0.620 (0.05)	0.662 (0.08)	< 0.005 †‡

Normalized hydraulic diameter (D_h*)

	Healthy subjects	Non-severe asthmatics	Severe asthmatics	Kruskal-Wallis tests (P value)
RB9+10	0.389 (0.06)	0.358 (0.07)	0.345 (0.07)	< 0.001 ‡
sRML	0.280 (0.04)	0.261 (0.05)	0.251 (0.05)	< 0.001 *‡
sRLL	0.303 (0.04)	0.281 (0.05)	0.274 (0.05)	< 0.005 *‡
TriLLB	0.485 (0.06)	0.456 (0.06)	0.446 (0.08)	< 0.005 *‡
sLLL	0.338 (0.04)	0.316 (0.05)	0.307 (0.05)	< 0.001 *‡

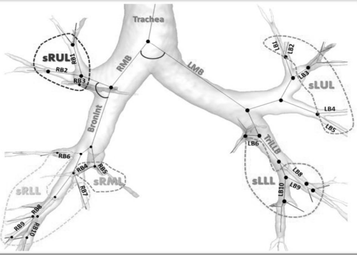


Values are presented as mean (SD).
*: Healthy vs. Non-severe asthma
†: Non-severe asthma vs. Severe asthma
‡: Healthy vs. Severe asthma

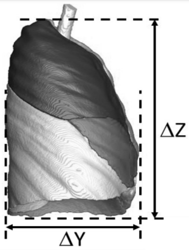
S Choi et al. (2015) *J Appl Physiol*, Quantitative assessment of multiscale structure…

MULTISCALE IMAGING-BASED CLUSTERING

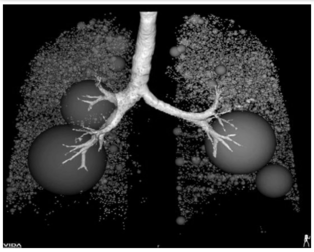
Local structures: θ, *Cr*, WT*, and D_h* (10 regions, 32 variables)



Global structure: Lung shape (1 variable)

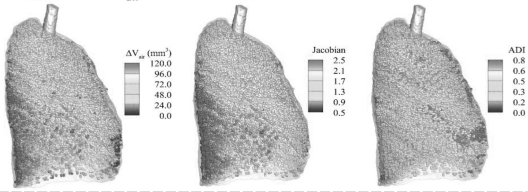


Global (lobar) function: AirT% (6 variable)



Registration-derived global (lobar) functions (18 variables)

U/(M+L)|v, and ΔV_{air}^F Jacobian ADI



57 variables

Principal component analysis to obtain **linearly uncorrelated variables**

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IMAGING AND CLINICAL CHARACTERISTICS

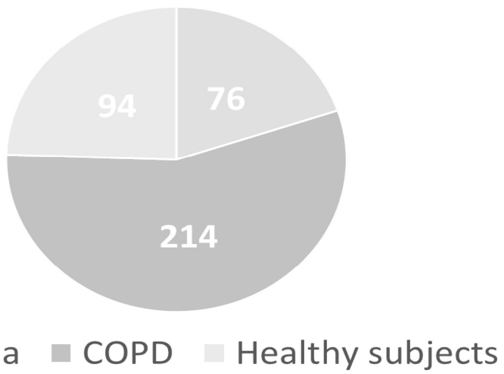
	Imaging characteristics	Clinical characteristics
Cluster 1	• Normal airway structure • Increased lung deformation (Jacobian and ADI↑)	• Younger, early onset • Nonsevere asthma • Reversible lung function • Easy to control asthma symptoms
Cluster 2	• Airway luminal narrowing (D_h*↓) • No airway wall thickening (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

S Choi et al. (2017) *JACI*, Quantitative computed tomographic imaging–based clustering...

APPLICATIONS OF MULTISCALE QCT IMAGING-BASED METRICS

- ✓ **Deep learning for classification of healthy subjects, asthma and chronic obstructive pulmonary disease (COPD).**

Humans subjects data sets



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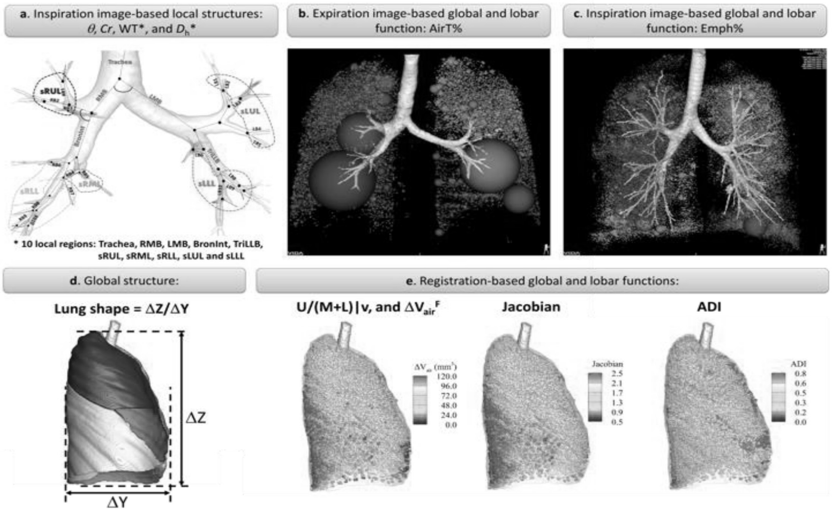
Methods

QCT Multiscale Imaging-based variables



- **75 QCT imaging variables** including airway diameter, wall thickness, air trapping, lung shape, air-volume change, Jacobian, ADI, and more [1].

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Preliminary Results

✓ As a result of **28,000 iterations** in training data, it has a loss of less than **0.1** and **an accuracy of 99%.**

✓ In testing data, we obtained the **same accuracy of 87%** as increasing the number of layers.

Layer(s)	One	Two	Three	Four
Accuracy	87%	87%	87%	87%
Time(s)	10.5	11.9	13.5	16.0

✓ This study demonstrates the potential of deep learning technique to serve as a simple but highly competitive method for **classifying respiratory diseases**.

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KOREAN DATASETS

	Processed subjects	Females	Males	Smokers (Former+ Current)	Non-smokers
Healthy subjects	**260**	144	116	69	191
Asthmatic patients	**63**	43	20	15	48
Total	**323**	**187**	**136**	**84**	**239**

✓ **QCT Imaging metrics could be expanded for multiple studies of Korean subjects**

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Caucasian vs. Asian (Korean)

✓ **Extracted only non-smoker healthy females**

- SARP (Severe Asthmatic Research Program): **31 subjects**
- SNUH (Seoul National University Hospital): **31 subjects**

	Caucasian	Asian (Korean)	P value (T-test)
Age (years)	38.7 (14.5)	40.5 (13.2)	0.6
Height (cm)	164 (6.0)	159 (6.4)	4.2×10^{-3}
Weight (kg)	66.7 (12.6)	57.7 (6.6)	0.0028
BMI (kg/m^2)	24.7 (4.1)	22.8 (2.7)	0.07

Caucasian vs. Asian (Korean)

- ✓ **Comparison of airway structure and function using QCT imaging metrics**

	Caucasian	Asian (Korean)	P value (T-test)
TLC (liters)	4.24 (0.64)	**3.17 (0.63)**	< 0.001
FRC (liters)	1.74 (0.52)	1.91 (0.52)	0.11
IC (liters)	2.30 (0.52)	**1.26 (0.60)**	< 0.001
D_h at sLLL (mm)	5.3 (0.6)	**4.6 (0.5)**	< 0.001
fSAD%(RLL)	0.9%(0.4%)	**2.5%(0.9%)**	0.04
U/(M+L)|v	60 (8.7)	**74 (14.1)**	< 0.001

- ✓ **Lung function reduction in lower lobes of Korean!**

Image analysis Menopause vs. Menstruation

- **Non-smoker healthy subjects**
  - SARP (Severe Asthmatic Research Program)

	Women			Men		
	Old (>55)	Young (<45)	P value	Old (>55)	Young (<45)	P value
Subjects	29	43		25	28	
Age (years)	63.3 (7.2)	29.5 (8.3)	< 0.001	64.7 (6.5)	25.1 (5.5)	< 0.001
Height (cm)	163.4 (6.9)	164.7 (5.2)	0.37	174.9 (7.1)	177.9 (7.6)	0.14
Weight (kg)	70.8 (15.5)	70.0 (18.1)	0.86	87.8 (11.4)	84.6 (19.9)	0.47
BMI	26.5 (5.2)	25.8 (6.4)	0.63	28.8 (4.2)	26.6 (5.6)	0.11

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Image analysis Menopause vs. Menstruation

- ✓ In old women **(menopausal),** functional small airway disease (fSAD%) increased, whereas young women **(menstruation)** had significant smaller fSAD%. → Possibly due to Hormone effect.
- ✓ **Larger FRC volume** in menopausal women → An **increase of fSAD%** and an **increase of TLC** for compensatory function (hyperinflation).
- ✓ Only menopausal women (not in men) had **a decrease of volume change (Jacobian) in upper and middle lobes** (LUL, RUL and RML). → Possibly due to lung compliance decrease.

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Ms. Jiyoung Kim

NRF National Research Foundation of Korea

SPIROMICS

SARP THE SEVERE ASTHMA RESEARCH PROGRAM

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