

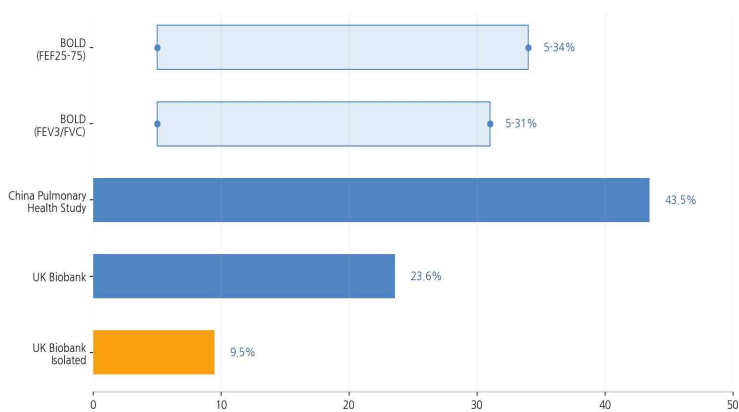
# Detection of Small Airway Disease in COPD

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*Severance*

# Prevalence of Small Airway Dysfunction in General Population



주: BOLD는 단일값이 아닌 범위(range)이며, 연구별 정의가 달라 직접 비교에 유의됨(%)

BOLD study (n = 28,604)

Small airways obstruction:  
spirometry findings  
( $FEF_{25\%-75\%} < LLN$  or  $FEV_3$  to FVC  
ratio  $< LLN$ )

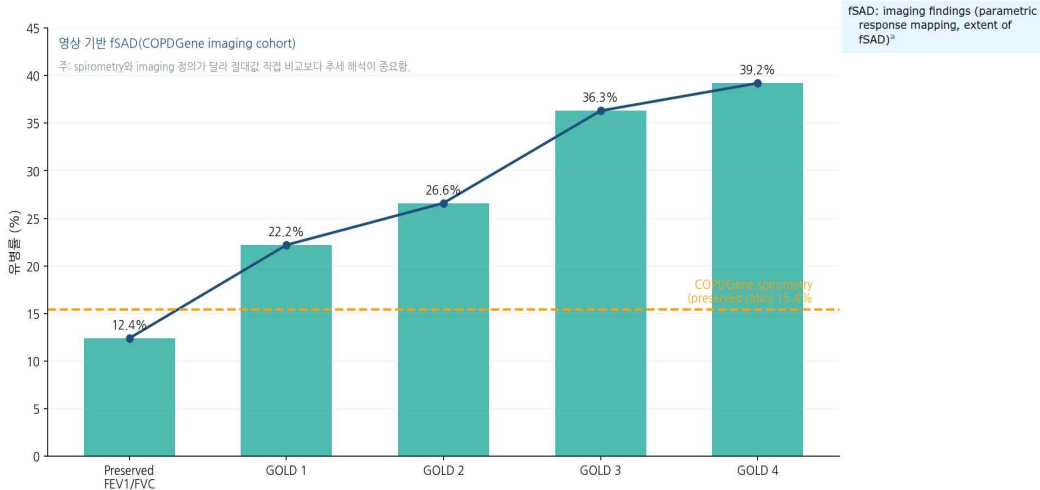
China Pulmonary Health  
Study Group (n = 50,479)

Small airways dysfunction:  
spirometry findings (at least 2 of  
 $FEF_{25\%-75\%}$ ,  $FEF_{50\%}$  or  
 $FEF_{75\%} < 65\%$  predicted)

UK Biobank (n = 252,877)

Small airways obstruction:  
spirometry findings ( $FEV_3$  to FVC  
ratio  $< LLN$ )

# Prevalence of SAD among Smokers: COPD gene cohort



# Airway Anatomy & Physiology

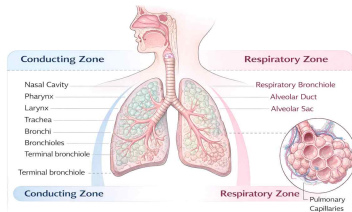
## ⇒ Large Airways

- Trachea ~ 8th generation
- Supported by cartilage to prevent collapse
- Despite larger caliber, contribute the **majority (>80%)** of **total airway resistance** in healthy lungs

## ⌘ Small Airways

- Distal conducting airways < 2 mm diameter (generations ~8-23)
- Lack cartilaginous support
- Patency depends on lung elastic recoil
- **"silent zone"** : massive total **cross-sectional area** and **minimal contribution to total resistance** until disease is advanced

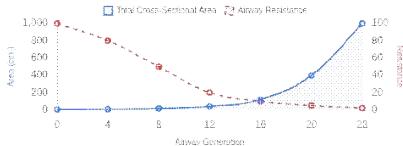
Weibel's Model of Airway Generations



Gen 0 - 16  
Anatomic Dead Space

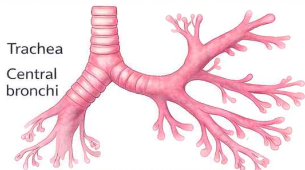
Gen 17 - 23  
Gas Exchange

Cross-Sectional Area vs. Resistance



# Airway Resistance Distribution

## Large (Central) Airways



Resistors in Series

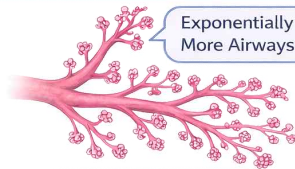


Like Resistors in Series

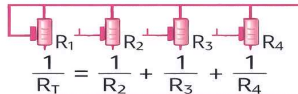
$$R_T = R_1 + R_2 + R_3 + R_4$$

vs.

## Small Airways



Resistors in Parallel



Like Resistors in Parallel

$$\frac{1}{R_T} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4}$$

Small airways = silent zone

# **I N D E X**

- **Spirometry**
- **Forced Oscillation Technique (FOT)**
- **Ventilation Heterogeneity**
- **Radiologic Assessment**
- **Clinical implication of SAD in COPD**

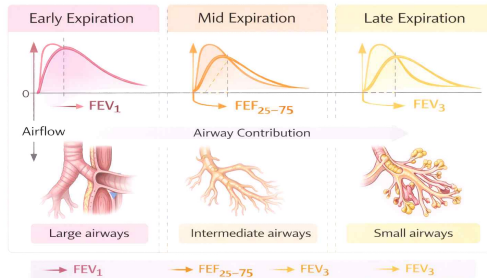
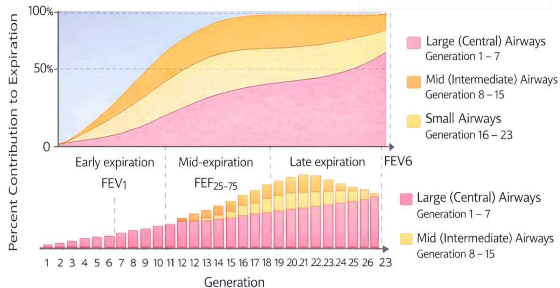
# Spirometry

# Spirometry Key Parameters & Interpretation

Parameter	Symbol/Formula	Clinical Meaning
FEV <sub>1</sub>	Forced expiratory volume in 1 second	Reflects degree of airflow limitation (severity)
FVC	Forced vital capacity	Suggests restriction when reduced Often normal in pure obstruction; reduced in air trapping (pseudorestriction).
FEV <sub>1</sub> /FVC	Ratio	Core for obstruction (below LLN or < <b>0.70</b> )
PEF	Peak expiratory flow	Sensitive drop in upper/central airway obstruction <i>Reflects caliber of large airways; effort-dependent.</i>
FEF50%/FIF50%	Flow ratio at 50% of lung volume	> <b>1</b> variable extrathoracic, < <b>0.5</b> variable intrathoracic obstruction
Empey Index	FEV <sub>1</sub> (L) ÷ PEF (L/s)	> <b>10</b> strongly suggests upper/central airway obstruction (UAO)

LLN: lower limit of normal; UAO: upper airway obstruction

# Regional Contribution of Large and Small Airways to Expiratory Flow



# Spirometric Indices for Small Airways

## Traditional Parameters

↵ **FEF<sub>25-75%</sub> (MMEF)** Mid-expiratory Flow

**Most sensitive** spirometric indicator for small airway obstruction, though **highly variable**.

↵ **FEF<sub>50%</sub> & FEF<sub>75%</sub>** Instantaneous Flow

FEF<sub>75%</sub> specifically **targets distal airways** but **effort-dependent** and **less reproducible**

⚖️ **Emerging Ratios** New Metrics

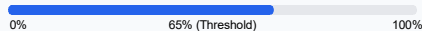
**FEV<sub>3</sub>/FVC** and **FEV<sub>3</sub>/FEV<sub>6</sub>** offer **better reproducibility**.  
Lower Limit of Normal (**LLN**) should be used over fixed cut-offs.

## Clinical Interpretation

### ⚠️ High Variability Warning

FEF<sub>25-75%</sub> has a wide normal range.

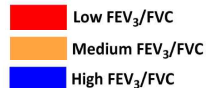
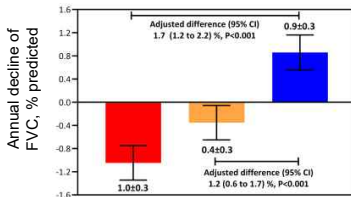
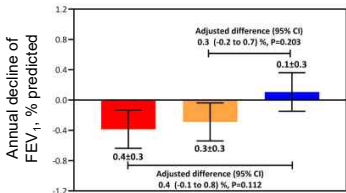
A value must often be **<60-65% predicted** to be considered abnormal.



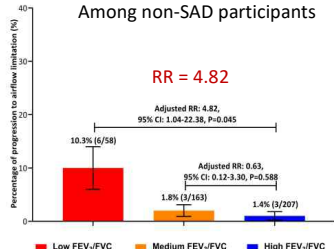
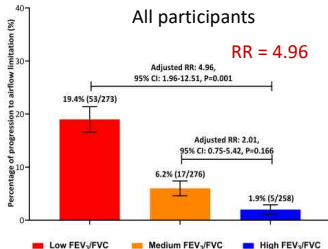
"Scooped" appearance indicates distal obstruction

# Reduced FEV<sub>3</sub>/FVC as an Early Indicator of COPD

## 3-year community-based cohort study

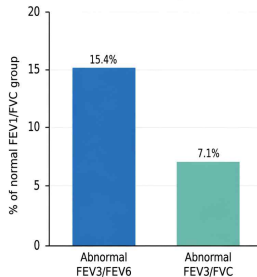


SAD: at least two of three post-bronchodilator metrics ( FEF 50%, FEF75%, or FEF25-75%) below 65% of predicted

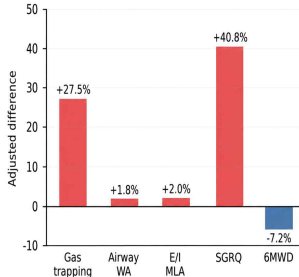


# A Novel Spirometric Measure Identifies Mild COPD Unidentified by Standard Criteria (COPD Gene)

Hidden abnormality detection



Adjusted impact of isolated low FEV3/FEV6



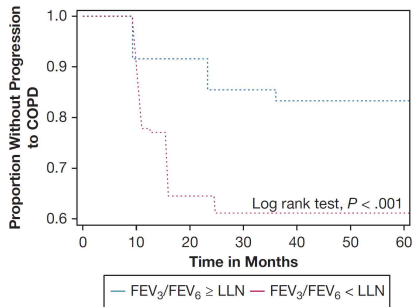
Outcome	FEV3/FEV6 ≥ LLN	FEV3/FEV6 < LLN	P
Gas trapping, %	8.6	10.8	<.0001
E/I MLA	0.83	0.85	<.0001
Segmental airway WA, %	60.3	61.4	<.0001
SGRQ total score	10.4	19.9	<.0001
mMRC dyspnea score	0.8	1.2	<.0001
6MWD, m	444	415	<.0001

Low FEV3/FEV6 identifies a clinically and structurally impaired smoker subgroup despite normal FEV1/FVC, supporting its value as an early small-airway disease marker.

# FEV<sub>3</sub>/FEV<sub>6</sub> in Recognition of Early Airway Disease (SPIROMICS)

The LLN for FEV<sub>3</sub>/FEV<sub>6</sub> approximately 0.93 at age 40 years to approximately 0.89 at age 80 years repeated 6 weeks following the baseline intraclass correlation was 0.97 for FEV<sub>1</sub>, 0.98 for FEV<sub>3</sub>, and 0.98 for FEV<sub>6</sub>, indicating excellent agreement between repeat measurements

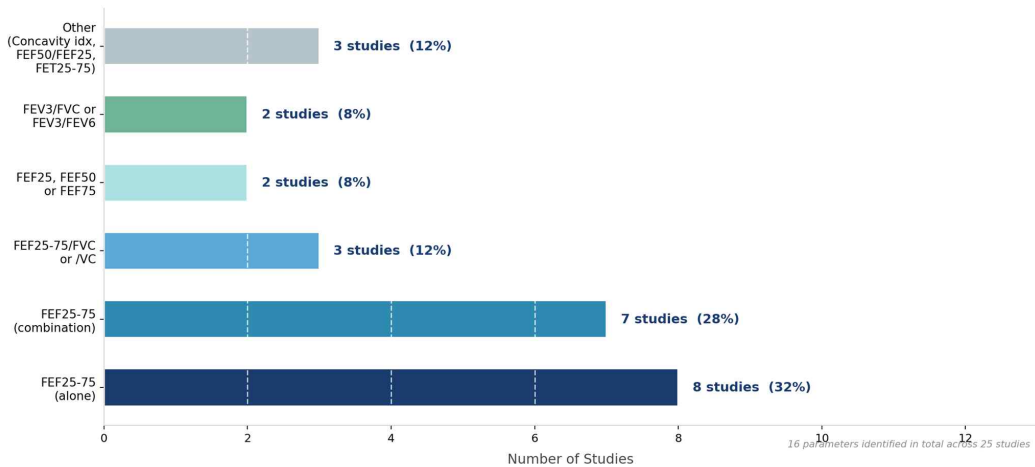
COPD Outcome Measure (FEV <sub>3</sub> /FEV <sub>6</sub> Less than the LLN vs FEV <sub>3</sub> /FEV <sub>6</sub> at or Above the LLN)	Hazard Ratio
	Adjusted <sup>b</sup>
Time to first exacerbation <sup>f</sup>	1.52 (1.02-2.25; <i>P</i> = .039)
Risk of progression to COPD by GOLD criteria <sup>g</sup>	2.11 (1.48-3.03; <i>P</i> < .001)



Baseline Variable	FEV <sub>3</sub> /FEV <sub>6</sub> Less Than the LLN (n = 143)	FEV <sub>3</sub> /FEV <sub>6</sub> at or Above the LLN (n = 689)	<i>P</i> Value
SGRQ	29.1 ± 21.1	23.2 ± 18.3	.003
6MWD, m	428.3 ± 99.5	439.0 ± 95.8	.27
PRM <sup>Emph</sup> , %	0.7 ± 1.2	0.4 ± 0.8	.001
PRM <sup>fSAD</sup> , %	9.3 ± 9.5	7.8 ± 9.1	.017

# Spirometry parameters used to define small airways obstruction in population-based studies: systematic review

25 studies



# Spirometry parameters used to define small airways obstruction in population-based studies: systematic review

## Population-based studies estimating prevalence of small airways obstruction

Study	Parameter Used	Cut-off	Criteria
Detels et al. (1979)	FEF		predicted
Wipf et al. (1982)			$C < FEV_1/VC$
Marazzini et al. (1989)			50% pred / $FEF_{25} < 65%$ 130% pred
Cullinan et al. (1997)			quartile (<67% predicted)
Nemoto et al. (2011)			
Lam et al. (2012)			
Chen et al. (2013)		< 70% predicted	
Hansen et al. (2015)	$FEV_3/FVC, FEV_3/FEV_6$	< LLN	
Johns et al. (2017)	$FEF_{25-75}$ , Concavity Index	$FEF_{25-75} < LLN$ ; Concavity > ULN	
Xiao et al. (2020)	$FEF_{25-75}$ , $FEF_{50}$ , $FEF_{75}$ , $FEV_3/FVC$	2/3 abnormal OR $FEV_3/FVC < LLN$	

### Cut-off Criteria Used

- < LLN (Lower Limit of Normal) [13 studies] — most rigorous
- < 65% predicted [6 studies] — commonly used
- < 70% predicted [5 studies] — less conservative
- < 75% predicted [4 studies] — oldest criterion
- Other (ratios, quartiles) [5 studies] — heterogeneous

# Effect of Spirometry Parameter Choice and WHO Region on Pooled Small Airways Obstruction Prevalence

## Meta-Regression Results (Random-Effects Model)

Variable	Coefficient (% change in prevalence)	95% CI	p value
<b>Spirometry Parameter (Reference: FEF25-75)</b>			
FEF25-75 (Reference)	—	—	—
FEF25-75 / VC	+14.3%	-10.0, +38.6	0.250
FEF50 / FEF25	-9.7%	-13.4, -5.9	<0.001
FEV3 / FVC	-5.7%	-9.3, -2.1	0.002
FEF50	+19.3%	+15.6, +23.1	<0.001
<b>WHO Region (Reference: Americas)</b>			
Americas (Reference)	—	—	—
European Region	+24.3%	+3.0, +45.6	0.025
Western Pacific	+5.3%	+3.0, +7.5	<0.001
South-East Asia	+4.1%	-18.7, +26.9	0.726

FEF<sub>25-75</sub>: mean expiratory flow<sub>25-75</sub>% FVC | FEF<sub>25-75</sub>/VC: FEF<sub>25-75</sub> as ratio of VC | FEF<sub>50</sub>: flow at 50% FVC  
 FEF<sub>50</sub>/FEF<sub>25</sub>: FEF<sub>50</sub> as ratio of FEF<sub>25</sub> | FEV<sub>3</sub>/FVC: FEV in 3 s / FVC | Bold = p<0.05 (significant)

## Parameter Effect on Prevalence

**FEF<sub>50</sub> yields HIGHEST prevalence (+19.3% vs FEF25-75)**

**FEF<sub>50</sub>/FEF<sub>25</sub> yields LOWEST prevalence (-9.7% vs FEF25-75)**

FEF<sub>25-75</sub>/VC: no significant difference (p=0.250)

FEV<sub>3</sub>/FVC: moderately lower (-5.7%, p=0.002)

=> **Parameter choice is the single biggest driver of SAO prevalence**

## Regional Effect on Prevalence

**European studies report HIGHEST prevalence vs Americas (+24.3%)**

Western Pacific: significantly higher (+5.3%, p<0.001)

South-East Asia: not significantly different (p=0.726)

=> **Geographic variation** partially reflects ethnicity, airway anatomy, & environment

## Clinical Takeaway

**SAO prevalence is not comparable across studies using different parameters**

**Standardization of parameter + cut-off is ESSENTIAL before policy use**

**LLN-based FEF<sub>25-75</sub>** is the most common approach but consensus still lacking

# Limitations of Spirometry in SAD



## Low Sensitivity

"Normal spirometry does not rule out SAD"



## High Variability

"Wide confidence intervals limit utility"



## Volume Dependence

"Flows must be interpreted relative to volume"

**~30%**

### Silent Disease

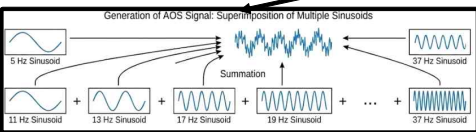
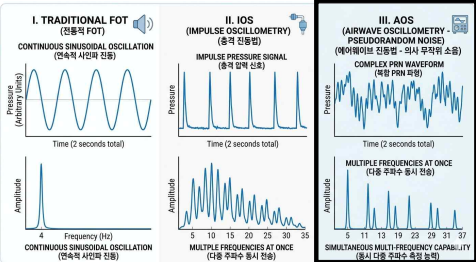
of symptomatic patients with normal spirometry have SAD on oscillometry/imaging.



**Spirometry** should be viewed as a **screening tool** rather than a definitive diagnostic test for **small airway disease**. **Normal results in symptomatic patients** warrant **further investigation** with oscillometry (IOS), body plethysmography, or high-resolution imaging.

# **Forced Oscillation Technique (FOT)**

# Forced Oscillation Technique (FOT)



Feature	IOS	AOS
Signal type	Impulse pressure signals	Continuous sinusoidal waves
Measurement principle	Fourier decomposition of impulses	Steady-state analysis
Acquisition speed	<b>Faster</b>	Slower
Signal stability	Moderate (more noise-sensitive)	<b>High (low noise)</b>
Reproducibility	Moderate	<b>High</b>
Sensitivity to breathing pattern	Higher	<b>Lower</b>
Frequency assessment	Broadband (simultaneous)	Frequency-by-frequency
Clinical use	<b>Widely used</b> in clinical practice	Emerging / <b>research-oriented</b>

# Impulse Oscillometry (IOS) Principles

## Core Mechanism

Superimposes **multi-frequency pressure impulses** (typically 5–35 Hz) on top of normal tidal breathing. **No forced maneuvers** required, making it ideal for pediatric, geriatric, and neuromuscular patients.

## Key Outputs

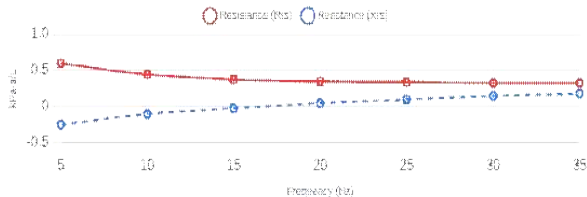
**Resistance (Rrs):** Energy dissipation in airways. Frequency-dependent (R5 vs R20).

**Reactance (Xrs):** Energy storage (elastic/inertial properties). Reflects peripheral compliance and stiffness.

### Clinical Advantage

*"Uniquely sensitive to peripheral airway mechanics ('silent zone') often missed by conventional spirometry."*

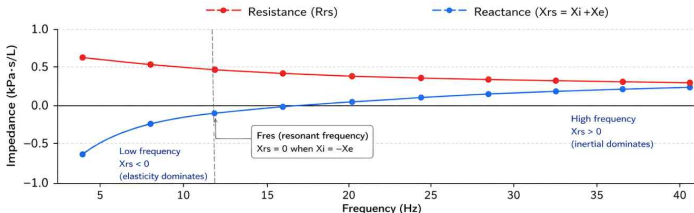
## Impedance Spectrum Example



	Phase	Reactance
Elastic	flow <b>lead</b>	negative
Inertial	flow <b>lag</b>	positive

# IOS Parameters: Definitions & Significance

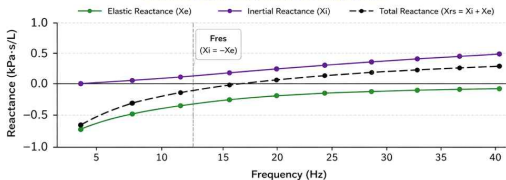
## Impedance and Reactance Across Frequencies



### Key Points

- At low frequencies, elastic effect ( $Xe$ , negative) dominates  $\rightarrow Xrs < 0$
- At high frequencies, inertial effect ( $Xi$ , positive) dominates  $\rightarrow Xrs > 0$
- Fres is the frequency where  $Xrs$  crosses zero ( $Xi = -Xe$ )
- COPD shifts Fres to higher frequencies (more negative  $Xe$  due to increased elastic load)

## Elastic and Inertial Reactance Components



**Inertial Reactance ( $Xi$ )**

- Positive (inductive behavior)
- Pressure precedes flow (flow lags)
- Increases approximately in proportion to frequency ( $\propto f$ )

**Elastic Reactance ( $Xe$ )**

- Negative (capacitive behavior)
- Flow precedes pressure (flow leads)
- Decreases in magnitude inversely with frequency ( $\propto 1/f$ )

Typical Values (kPa-s/L)			
Frequency (Hz)	$Xe$ (elastic)	$Xi$ (inertial)	$Xrs = Xi + Xe$ (total)
5	-0.60	+0.03	-0.57
10	-0.30	+0.06	-0.24
15	-0.20	+0.10	-0.10
20	-0.13	+0.16	+0.03 $\approx 0$ (Fres)
25	-0.09	+0.21	+0.12
30	-0.07	+0.27	+0.20
35	-0.06	+0.33	+0.27
40	-0.05	+0.40	+0.35

### Clinical Relevance

- More negative  $Xe$  and higher Fres are associated with increased small airway closure, air trapping, and peripheral airway disease.
- IOS parameters related to reactance: X5 (more negative), AX (area of reactance), Fres (higher in disease).

Normal: Fres ~ 8-12 Hz  
COPD: Fres ~ 15-25 Hz

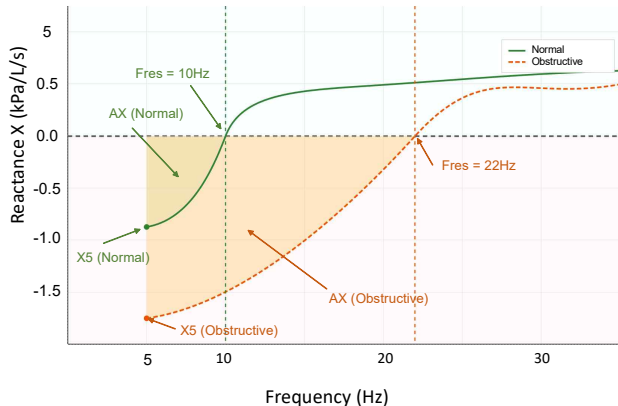
# IOS Parameters: Definitions & Significance

PARAMETER	DEFINITION	CLINICAL SIGNIFICANCE	TYPICAL UNIT
<b>R5</b>	Total respiratory resistance at 5 Hz.	Reflects total airway resistance ( <b>large + small airways</b> ). Elevated in overall obstruction.	0.3-0.5 kPa/L/s
<b>R20</b>	Resistance at 20 Hz (proximal airways).	Reflects <b>central/large airway resistance</b> . Often normal in isolated small airway disease.	0.2-0.4 kPa/L/s
<b>R5 - R20</b>	Frequency dependence of resistance.	<b>Key index for small airway dysfunction</b> . High values indicate distal obstruction/heterogeneity.	< 0.07 kPa/L/s (< 20% of R5)
<b>X5</b>	Reactance at 5 Hz (distal capacitive load)	Reflects <b>elastic recoil of peripheral lung</b> . More negative in fibrosis or hyperinflation.	-0.1 to -0.3 kPa/L/s
<b>Fres</b>	Resonant Frequency (Reactance = 0)	Point where inertance equals capacitance. <b>Shifted right</b> (higher Hz) in airway obstruction.	8-12 Hz
<b>AX</b>	Area of Reactance (low frequency).	Integrated low-frequency reactance area. highly sensitive index of total respiratory impedance.	< 1.0 kPa/L

*R5-R20 and AX are often more sensitive than FEV1 for detecting early peripheral airway disease.*

# Fres & AX in Impulse Oscillometry

## Resonant Frequency and Reactance Area as Small Airway Disease Markers



### What is Fres?

Frequency where Reactance  $X = 0$   
 Elastic recoil force = Air inertance force  
 Normal adults: 7–12 Hz  
 Formula:  $Fres = 1 / (2\pi\sqrt{LC})$   
 $L$  = Inertance |  $C$  = Compliance  
 Disease: Fres  $\uparrow$  (shifts RIGHT on graph)

### What is AX?

Area under Reactance curve (below zero)  
 Integrated from 5 Hz  $\rightarrow$  Fres  
 Combines X5 depth + Fres shift  
 Normal: AX < 1.0 kPa/L  
 Obstruction: AX  $\uparrow\uparrow$  (2–5 kPa/L)

	Normal	Obstruction
<b>Fres</b>	7–12 Hz	> 12-15 Hz $\uparrow$
<b>X5</b>	-0.1~-0.2 kPa/L/s	< -0.3 - -0.5 kPa/L/s $\downarrow\downarrow$
<b>AX</b>	< 1.0 kPa/L	> 1.0-1.5 kPa/L $\uparrow\uparrow$

AX  $\uparrow$  when both X5  $\downarrow$  AND Fres  $\uparrow$  — AX is a composite marker of peripheral airway dysfunction

## Quick guide for interpreting IOS patterns

### 🏠 **Small Airway Disease**

Normal R20, ↑ (R5-R20),  
↓ X5 (more negative)

### 🚧 **Central Obstruction**

↑ R5, ↑ R20,  
Normal (R5-R20)

### ⊗ **Restriction / Fibrosis**

↓ X5 (stiff lung), ↑  
Fres, R5 often normal

### ✔ **Response to Therapy**

↓ R5, ↓ AX, ↓ Fres  
post-bronchodilator

**TABLE IV.** Characteristics of healthy controls and symptomatic patients with PPF and SAD defined as  $FEF_{25\%-75\%} < 65\%$  predicted (N = 43)\*

Characteristic	Healthy controls (N = 43)	Symptomatic patients with PPF and SAD (N = 43)	P value
Age (y)	55 (42-63)	57 (46-66)	0.47
Sex: male, n (%)	21 (48.84)	21 (48.84)	1
Height (cm)	165 (159-172)	164 (156-170)	0.39
Smoking, n (%)	0 (0.00)	10 (23.26)	<0.01
FEV <sub>1</sub> (% predicted)	101.24 (94.12-108.52)	86.89 (82.05-92.25)	<0.01
FVC (% predicted)	101.14 (89.56-107.99)	92.94 (85.16-101.23)	0.02
FEF <sub>25%-75%</sub> (% predicted)	83.47 (72.65-100.07)	53.55 (45.71-59.26)	<0.01
R <sub>5</sub> - R <sub>20</sub> [kPa/(L/s)]	0.07 (0.04-0.09)	0.09 (0.05-0.15)	0.03
X <sub>5</sub> [kPa/(L/s)]	-0.09 (-0.13 to -0.07)	-0.11 (-0.14 to -0.08)	0.11
F <sub>res</sub> (Hz)	13.14 (10.53-14.9)	15.33 (13.36-18.92)	<0.01
AX (kPa/L)	0.34 (0.16-0.57)	0.49 (0.28-1.05)	<0.01

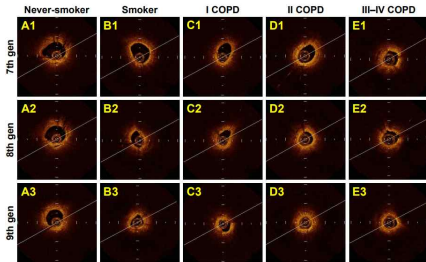
PPF: preserved pulmonary function

Change in Airway Peripheral Tone in COPD (CAPTO-COPD) trial

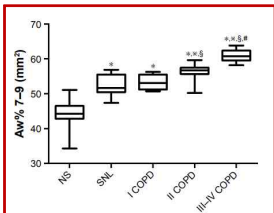
**Table 3** Spirometry, IOS and questionnaire results at the study visit. Means with standard deviations are shown for continuous variables and numbers and percentages are shown for categorical variables. For IOS variables geometric means (adjusted for gender and age) are shown. PN = predicted normal value. Letters a, b, c and d show pair wise significant comparisons between indicated groups ( $p < 0.05$ ). (Q+/- = self-reported chronic bronchitis or emphysema or COPD or not, G+/- = COPD according to GOLD or not).

	Q-/G- (a) (n = 252)	Q-/G+ (b) (n = 90)	Q+/G- (c) (n = 43)	Q+/G+ (d) (n = 34)
FEV <sub>1</sub> % PN	105 <sup>b,c,d</sup> (13)	87 <sup>a,c,d</sup> (13)	100 <sup>a,b,d</sup> (15)	78 <sup>a,b,c</sup> (25)
VC% PN	110 <sup>c</sup> (14)	111 <sup>c</sup> (16)	105 <sup>a,b</sup> (16)	108 (22)
FEV <sub>1</sub> /VC	0.78 <sup>b,d</sup>	0.64 <sup>a,c,d</sup>	0.79 <sup>b,d</sup>	0.58 <sup>a,b,c</sup>
FEV <sub>1</sub> /VC% PN	102 <sup>b,d</sup> (6)	83 <sup>a,c,d</sup> (7)	102 <sup>b,d</sup> (7)	76 <sup>a,b,c</sup> (16)
R5 (kPa/(L/s))	0.29 <sup>b,c,d</sup>	0.32 <sup>a,d</sup>	0.35 <sup>a</sup>	0.39 <sup>a,b</sup>
R20 (kPa/(L/s))	0.23 <sup>c,d</sup>	0.24	0.25	0.27 <sup>a</sup>
R5-R20 (kPa/(L/s))	0.06 <sup>c,d</sup>	0.07 <sup>d</sup>	0.08 <sup>a</sup>	0.10 <sup>a,b</sup>
X5 (kPa/(L/s))	0.08 <sup>b,c,d</sup>	0.09 <sup>a,d</sup>	0.10 <sup>a,d</sup>	0.13 <sup>a,b,c</sup>
AX	0.19 <sup>b,c,d</sup>	0.27 <sup>a,d</sup>	0.31 <sup>a,d</sup>	0.55 <sup>a,b,c</sup>
Symptoms of CB	18 <sup>c,d</sup> (7.1%)	12 <sup>c</sup> (13.3%)	15 <sup>a,b</sup> (34.9%)	9 <sup>a</sup> (26.5%)
Long-standing cough	36 <sup>c,d</sup> (14.3%)	13 <sup>c,d</sup> (14.4%)	17 <sup>a,b</sup> (39.5%)	13 <sup>a,b</sup> (38.2%)
Any use of pulmonary medication	5 <sup>b,c,d</sup> (2.0%)	7 <sup>a,c,d</sup> (7.8%)	15 <sup>a,b</sup> (34.9%)	14 <sup>a,b</sup> (41.2%)

# IOS in Small Airway Dysfunction (SAD)

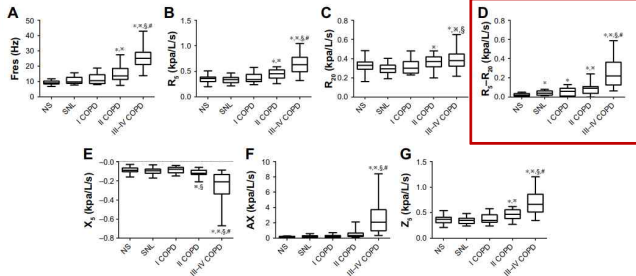


Endobronchial optical coherence tomography (EB-OCT)



Airway wall area percentage ( $A_w\%$ ) =  $[A_w / (A_i + A_w)] \times 100\%$   
 $A_i$  was corrected for the body surface area (BSA)

Comparisons of EB-OCT parameters of the 7<sup>th</sup> to 9<sup>th</sup> generation of bronchi among never-smokers, heavy smokers and patients with stages I-IV COPD



# IOS in Small Airway Dysfunction (SAD)

**Table S4** Correlation between EB-OCT parameters and IOS and spirometric indices in never-smokers, heavy-smokers and different stages of COPD

	Cases	FEV <sub>1</sub> % predicted		MMEF% predicted		Fres		R <sub>5</sub> -R <sub>20</sub>		
		r	P-value	r	P-value	r	P-value	r	P-value	
Aw% 7-9										
Never-smokers	21	-0.34	0.130	0.14	0.548	-0.27	0.246	-0.21	0.357	
Heavy-smokers	26	0.11	0.589	0.13	0.535	0.54	0.005	0.39	0.047	
Stage I COPD	17	0.09	0.729	0.24	0.348	0.49	0.047	0.37	0.141	
Stage II COPD	18	-0.37	0.130	-0.30	0.220	0.44	0.067	0.50	0.033	
Stage III COPD	19	-0.66	0.002	-0.45	0.056	0.51	0.026	0.37	0.118	
Stage IV COPD	5	-0.50	0.391	-0.20	0.747	0.90	0.037	0.30	0.624	
All COPD	59	-0.90	<0.001	-0.86	<0.001	0.83	<0.001	0.81	<0.001	

**Notes:** Data in boldface indicated the correlation with statistical significance. All *r* values denoted the Spearman's correlation coefficients.

**Abbreviations:** EB-OCT, endobronchial optical coherence tomography; MMEF, maximal mid-expiratory flow; IOS, impulse oscillometry; Aw%, airway wall area percentage =  $[Aw/(Ai+Aw)] \times 100\%$ ; 7-9, from 7th to 9th generation of bronchi; Fres, resonance frequency; R<sub>5</sub>-R<sub>20</sub>, the difference between airway resistance at 5 Hz and 20 Hz; FEV<sub>1</sub>, forced expiratory volume in the first second.

# Comparison of oscillometry ratios between IOS and AOS in patients with asthma and COPD

**Table 2**

Comparison of IOS vs AOS measurements.

AOS airwave oscillometry, BD bronchodilator (salbutamol 400 µg), CI confidence interval, ICC intra-class correlation coefficient, IOS impulse oscillometry, R5 resistance at 5 Hz, R20, resistance at 20Hz, AX area under the reactance curve, X5 reactance at 5 Hz.

	Ratio	Group	Correlation (r)	p-value	ICC (95 % CI)	Mean % difference (95 % CI)	p-value
<b>Pre BD</b>	<b>R5-R20(19)/R5</b>	All	0.84	<0.001	0.84 (0.76, 0.89)	-0.4 (-2.18, 1.38)	NS
		Asthma	0.85	<0.001	0.85 (0.75, 0.91)	-1.66 (-3.61, 0.29)	NS
		COPD	0.81	<0.001	0.79 (0.58, 0.91)	2.64 (-1.17, 6.45)	NS
	<b>X5/AX</b>	All	0.87	<0.001	0.56 (0.11, 0.77)	7.99 (5.95, 10.02)	<0.001
		Asthma	0.88	<0.001	0.57 (-0.06, 0.82)	9.01 (7.14, 10.96)	<0.001
		COPD	0.93	<0.001	0.53 (0.18, 0.76)	5.43 (0.07, 10.79)	<0.05
<b>Post BD</b>	<b>R5-R20(19)/R5</b>	All	0.80	<0.001	0.79 (0.69, 0.86)	1.10 (-0.78, 2.98)	NS
		Asthma	0.71	<0.001	0.70 (0.54, 0.81)	0.95 (-1.35, 3.25)	NS
		COPD	0.86	<0.001	0.82 (0.62, 0.92)	1.47 (-2.03, 4.98)	NS
	<b>X5/AX</b>	All	0.82	<0.001	0.54 (0.07, 0.77)	10.15 (7.69, 12.62)	<0.001
		Asthma	0.81	<0.001	0.52 (-0.03, 0.78)	11.95 (9.12, 14.78)	<0.001
		COPD	0.92	<0.001	0.49 (0.12, 0.74)	5.81 (1.01, 10.60)	<0.05

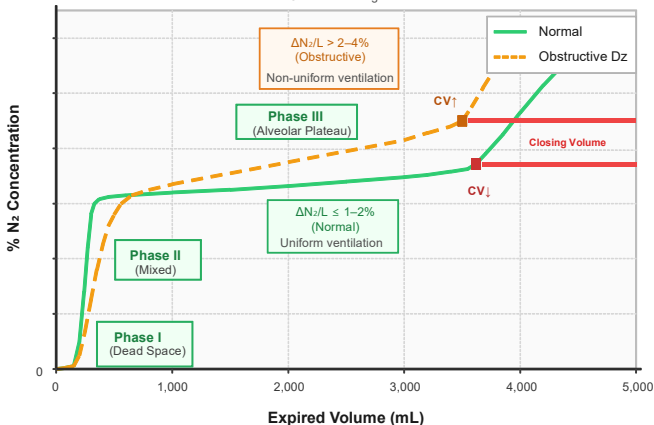
AOS and IOS provide highly comparable resistance-derived indices (R5–R20), whereas reactance-derived indices (X5 and AX) show strong correlations but significant systematic differences, indicating that device-specific reference values may be required.

# Ventilation Heterogeneity

# Single-Breath Nitrogen Washout Test

## Single-Breath Nitrogen Washout (SBN<sub>2</sub>) Curve

Normal vs. Obstructive Lung Disease



### ✓ Normal Findings

- Phase II: Sharp, rapid N<sub>2</sub> rise (150–350 mL)
- Phase III slope:  $\Delta N_2 \leq 1-2\%$  per liter
- Phase IV onset: ~75–80% of VC
- CV/VC ratio: < 10–20% (age-dependent)

### ⚠ Obstructive Findings

- Phase II: Prolonged, gradual rise
- Phase III slope:  $\Delta N_2 > 2-4\%/L$  ← key marker
- Phase IV onset: Earlier (↑ CV/VC ratio)
- Uneven V/Q & small airway dysfunction

### 🔍 Clinical Interpretation

- Phase III slope → small airway heterogeneity
- CV ↑ → air trapping, early airway closure
- SBN<sub>2</sub> detects SAD before spirometry changes
- Complements IOS/FOT in peripheral airway Dx

# Multiple Breath Washout (MBW) & Lung Clearance Index (LCI)

MBW assesses global ventilation heterogeneity

Measuring the washout of an inert tracer gas

\* N2: wash in with 100% O2

\* SF6: wash in with wash out with room air

1. Normal tidal breathing
2. 100% O<sub>2</sub> inhalation
3. Continue tidal breathing around FRC
4. Exhaled N<sub>2</sub> decreases until < 2.5%

Highly sensitive for early detection of structural lung disease when spirometry is normal.

Gold Standard

**Lung Clearance Index (LCI)**

Number of lung volume turnovers required to clear tracer gas to 1/40th of starting concentration. **LCI > 7.0** is typically abnormal.

$$LCI = \frac{\text{Cumulative expired volume (CEV)}}{\text{FRC}}$$

LCI Sensitivity vs. FEV1 in Early Disease

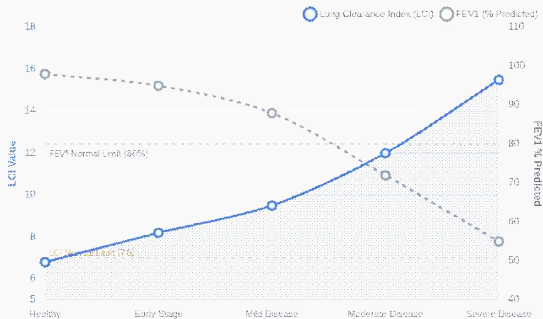


Fig 1. Progressive elevation of LCI in early disease stages while FEV1 remains within normal range.

# SBN<sub>2</sub> vs MBW

Feature	SBN <sub>2</sub>	MBW
Number of respiration	single breath	multiple breaths
Assessment	emptying pattern	washout efficiency
Index	Phase III slope, CV <b>Regional ventilation inequality</b>	LCI <b>Global ventilation heterogeneity</b>
Sensitivity	Modest	Very high
Advantages	-Short test time (1-2 min) -Based on Graph (Physiologically intuitive) -Assessment of small airway closure (CV, CC)	-Sensitive evaluation of SAD -Effort-independent -FRC is calculated during the test
Disadvantages	Cooperation (deep inspiration + controlled expiration) Difficult: Child, elderly, NM disease Single expiration, slow lung unit	Longer test time (10-20 min) Expensive diagnostic equipment (gas analyzer, flow measurement) LCI calculation

# Ventilation heterogeneity in COPD (MBW)

TABLE 2. LUNG FUNCTION AND MULTIPLE-BREATH WASHOUT RESULTS OBTAINED IN SMOKERS WITH 30 PACK-YEARS SMOKING HISTORY OR MORE

	Non-COPD (n = 25)		COPD/- (n = 26)		COPD/E (n = 27)	
	Mean	SE	Mean	SE	Mean	SE
Age, yr	48	1	60*	2	68*. <sup>†</sup>	2
Smoking history, pack-years	43	4	60	7	52	3
Lung function						
FEV <sub>1</sub> , % predicted	101	4	68*	3	51*. <sup>†</sup>	3
FEV <sub>1</sub> /FVC, %	77	1	57*	2	45*. <sup>†</sup>	2
FEF <sub>25-75r</sub> , % predicted	84	6	28*	2	17*	1
FEF <sub>75r</sub> , % predicted	64	5	22*	2	17*	1
DL <sub>CO</sub> , % predicted	84	2	82	2	47*. <sup>†</sup>	2
sGaw, 1/cm H <sub>2</sub> O · s	0.153	0.013	0.060*	0.004	0.050*	0.004
Multiple-breath washout						
S <sub>acinar</sub> L <sup>-1</sup>	0.149	0.016	0.295*	0.026	0.444*. <sup>†</sup>	0.037
S <sub>conduc</sub> L <sup>-1</sup>	0.043	0.003	0.064*	0.004	0.068*	0.006
FRC <sub>MBWr</sub> , ml	3284	143	3474	143	3884	139
FRCpl - FRC <sub>MBWr</sub> , ml	-92	64	675*	112	1278*. <sup>†</sup>	139

Acinar  
Conductance

Ventilation heterogeneity in COPD originates from both conductive and acinar airway dysfunction, with acinar ventilation heterogeneity (S<sub>acinar</sub>) showing the strongest association with emphysema severity.

# **Radiologic Assessment**

# HRCT Assessment of Small Airways

Paired Inspiratory and Expiratory Scans

## Inspiratory Scan



Often appears normal in mild small airway disease

## Expiratory Scan



Mosaic attenuation reveals functional air-trapping

## Radiographic Features

- Direct Visualization

Thickened bronchiolar walls, centrilobular nodules ("tree-in-bud"), and mucus plugging in bronchiolitis.

- Mosaic Attenuation

Patchy areas of low density on expiratory scans indicate air-trapping due to small airway obstruction, distinguishing it from vascular mosaicism.

- Quantitative CT (QCT)

Automated metrics like %LAA-950 (emphysema) and %LAA-856exp (gas trapping) provide objective functional data.

### Clinical Pearl:

*"Expiratory scans are essential. Inspiratory CT alone misses >50% of small airway disease cases in early COPD and asthma."*

# Parametric Response Mapping (PRM)

## Core Methodology

A voxel-by-voxel co-registration technique aligning inspiratory (full inflation) and expiratory (residual volume) CT scans.



### PRM<sub>Emph</sub> (Emphysema)

Low density on both inspiration and expiration (<-950 HU)



### PRM<sub>fSAD</sub> (Functional SAD)

Normal inspiratory density (>-950 HU) but low expiratory density (<-856 HU) indicating air trapping

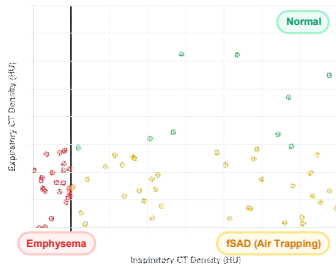


### PRM<sub>Normal</sub> (Healthy Parenchyma)

Normal density on both phases

	Inspiration HU	Expiration HU
Normal	> -950	> -856
fSAD	> -950	< -856
Emphysema	< -950	< -856

## PRM Voxel Classification Logic



**Clinical Impact: PRM<sub>fSAD</sub> is a strong independent predictor of FEV1 decline and progression to emphysema.**

# Quantitative CT Metrics



## Airway Wall Thickness (Pi10)

Square root of wall area for a hypothetical airway with 10mm internal perimeter. Standardizes measurements across variable airway sizes.

*Significance:* Strong correlate of airway remodeling and chronic bronchitis symptoms.



## Air Trapping Indices

Mean lung density ratio (E/I) or %LAA on expiratory scans (<-856 HU). Detects gas trapping due to small airway closure.

*Significance:* Sensitive marker for early small airway disease (SAD) before spirometric changes.



## Low Attenuation Areas (%LAA)

Percentage of lung volume below a density threshold (typically -950 HU). Quantifies extent of emphysematous destruction.

*Significance:* Directly correlates with DLCO impairment and hyperinflation.



## Lumen Dimensions

Direct measurement of luminal area (LA) and wall area percent (WA%). Focuses on segmental and subsegmental airways.

*Significance:* Predicts airflow limitation (FEV1) and exacerbation frequency.

## Clinical Utility

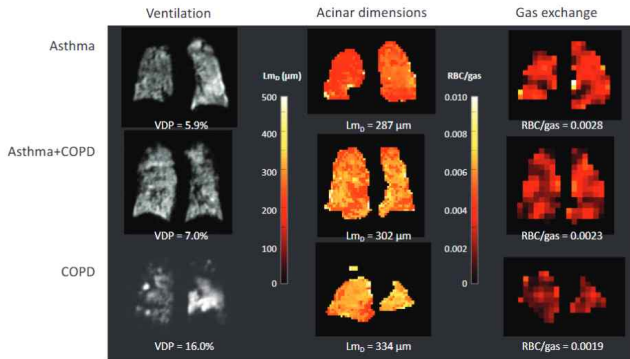
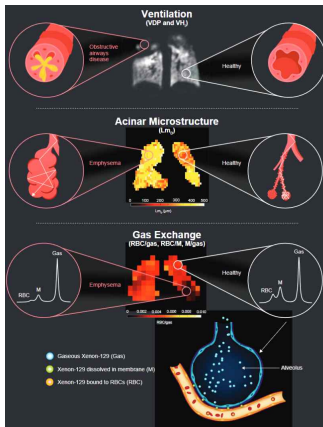
- ✓ **Phenotyping**  
Distinguishes predominant airway disease from emphysematous phenotypes in COPD.
- ✓ **Trial Endpoints**  
Increasingly used as objective endpoints in pharmaceutical trials for novel bronchodilators.
- ✓ **Correlation**  
Correlates well with functional metrics like oscillometry (R5-R20) and multiple breath washout (LCI).

## Key Insight

*"Quantitative CT provides a structural correlate to functional small airway impairment, offering a 'window' into the silent zone of lung disease."*

# 129Xe MRI and comprehensive physiologic testing

## Application of 129Xe MRI to assess functionality of lung ventilation, acinar microstructure, and gas exchange



Ventilation defect percent (VDP; percentage of unventilated lung), ventilation heterogeneity index (VH; the interquartile range of the coefficient of variation of signal intensity within ventilated regions), mean diffusible length scale ( $Lm_D$ ; a measure of acinar dimension), ratio of 129Xe dissolved in the red blood cells to 129Xe in the airspaces (RBC/gas), ratio of 129Xe dissolved in the alveolar membrane to 129Xe in the airspaces (M/gas), and ratio of 129Xe dissolved in the red blood cells to 129Xe in the alveolar membrane (RBC/M; Page 9 of 101 measures of alveolar gas exchange)

# **Clinical implication of SAD in COPD**

# Small Airway Disease (SAD)

## Detection and diagnosis

Early detection and Supplementary diagnostic tool

## Future exacerbation

SPIROMICS: CT-defined PRMfSAD and gas trapping predict consistent exacerbations

## FEV1 decline

COPDGene: PRMfSAD contributes more than emphysema in mild–moderate COPD

## Mortality

UK Biobank: FEV3/FEV6-defined SAO predicts all-cause and disease-specific mortality

## Treatment monitoring

Oscillometry/FOT tracks bronchodilator effects on hyperinflation and gas trapping

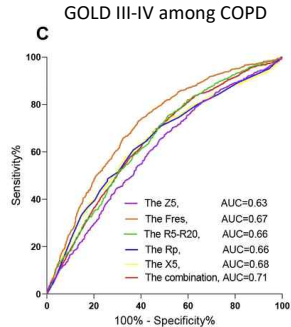
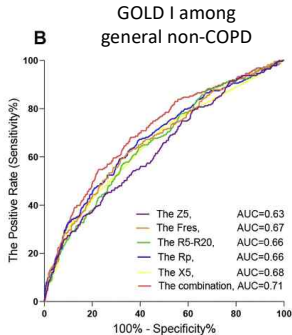
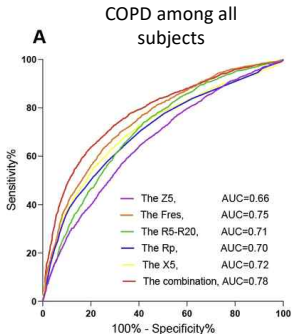
**SAD is not only an early physiologic abnormality; it helps identify patients at risk and can monitor treatment response.**

# Diagnostic Value of Impulse Oscillometry in COPD

6307 participants aged >40 years, comprising 2109 COPD patients and 4198 general non-COPD individuals

## KEY MESSAGES

- Fres showed the strongest overall association with airflow limitation
- X5 was the best single parameter for GOLD I COPD
- R5-R20 reflects peripheral airway narrowing
- IOS provides complementary information but cannot replace spirometry
- Combined IOS model AUC = 0.78

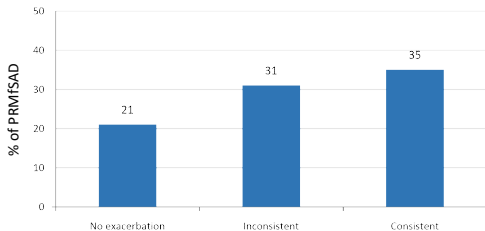


# Future exacerbation

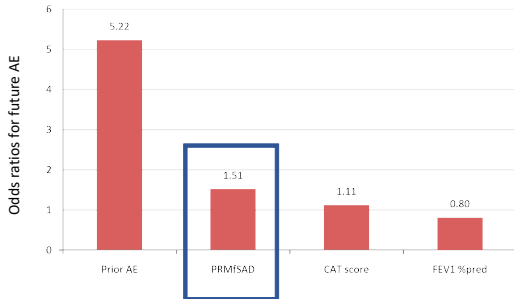
SPIROMICS COPD cohort with 3 years of prospective follow-up

SAD burden is higher in consistent exacerbators and SAD is a significant risk factor for future exacerbation

Baseline PRMfSAD by exacerbation group



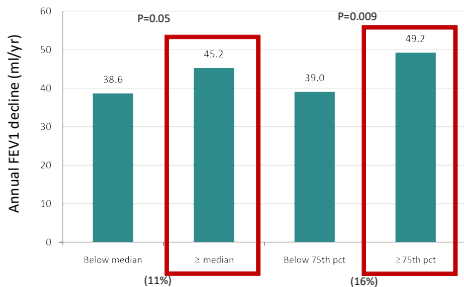
Stepwise logistic regression odds ratios



# Lung function decline: CT-defined fSAD predicts faster FEV1 loss

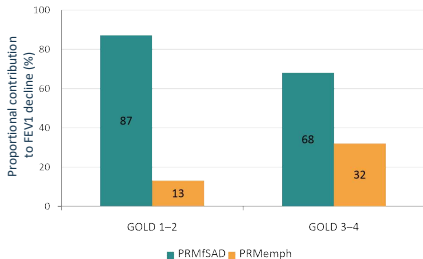
## COPDGene, 5-year longitudinal CT and spirometry

### Within GOLD 0: greater fSAD, faster decline



fSAD identifies high-risk smokers before classic obstruction

### Proportional contribution to FEV1 decline

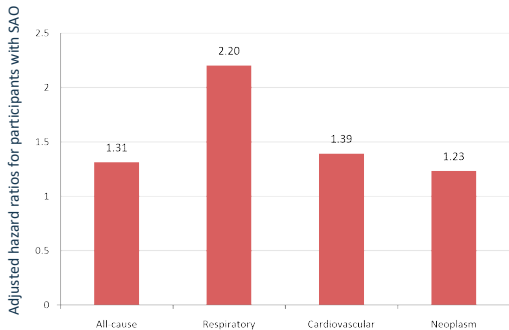


For early COPD, fSAD is a stronger progression signal than emphysema.

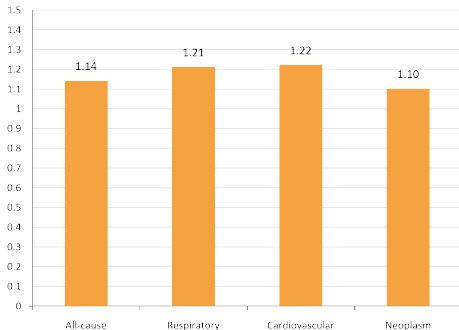
# Mortality: spirometry-defined SAO predicts survival outcomes

UK Biobank: FEV3/FEV6 < LLN, median follow-up 12.8 years

Adjusted hazard ratios for participants with SAO



Isolated SAO also carries risk



# Monitoring treatment response: SAD indices change with bronchodilation

## Oscillometry/FOT reflects hyperinflation and gas trapping response

### Correlations between FOT and lung-volume response

**Table 4.** Relationship between change in forced oscillation technique (FOT) and change in hyperinflation and gas trapping from baseline to 2 hrs post-long-acting bronchodilator.

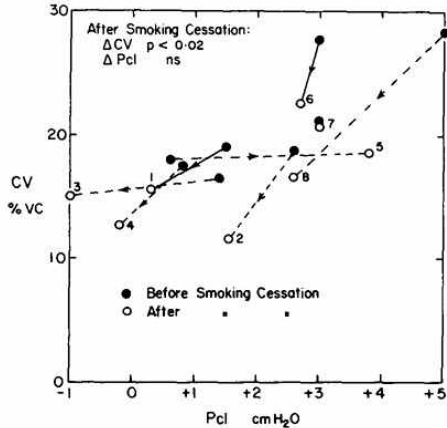
	$\Delta(\text{IC}/\text{TLC})$	$\Delta(\text{RV}/\text{TLC})$
Change in spirometry		
$\Delta\text{FEV}_1$	0.58*	-0.31
$\Delta(\text{FEV}_1/\text{FVC})$	0.07	0.37
Change in FOT parameters		
$\Delta\text{R5}$	-0.34	0.60*
$\Delta\text{R5}_{\text{in}}^{\text{S}}$	-0.51	0.75**
$\Delta\text{R19}$	-0.30	0.32
$\Delta\text{R5-R19}$	-0.40	0.70**
$\Delta\text{X5}$	0.48	-0.74**
$\Delta\text{X5}_{\text{in}}^{\text{S}}$	0.57*	-0.74**
$\Delta\text{AX}$	-0.54*	0.82**
$\Delta\text{X5}_{\text{in-ex}}^{\text{S}}$	-0.15	0.19

**Table 5.** Relationship between baseline forced oscillation technique (FOT), and subsequent change in hyperinflation and gas trapping 2 hrs post-long-acting bronchodilator.

	$\Delta(\text{IC}/\text{TLC})$	$\Delta(\text{RV}/\text{TLC})$
Spirometry <sup>§</sup>		
FEV1	-0.35	0.58*
Z-FEV1	-0.45	0.63*
FEV1/FVC	-0.47	0.64*
Z-FEV1/FVC	-0.43	0.68**
Adjusted FOT parameters <sup>^</sup>		
R5	0.59*	-0.74**
$\text{R5}_{\text{in}}^{\text{S}}$	0.53*	-0.59*
R19	0.44	-0.57*
R5-R19	0.61*	-0.61*
X5	-0.53*	0.60*
$\text{X5}_{\text{in}}^{\text{S}}$	-0.60*	0.50
AX	0.56*	-0.71**
$\text{X5}_{\text{in-ex}}^{\text{S}}$	0.62*	-0.76**

**Clinical interpretation: if FEV1 changes little, oscillometry may still show reduced gas trapping or small-airway load.**

# Therapeutic Approaches to Small Airway Disease



## Smoking cessation

- single breath nitrogen washout
- improvement of closing volume
- reversal of peripheral airway obstruction

# Whole lung directed anti-muscarinic therapy improves small airway dysfunction in COPD

## Study Overview

### Participants

43 symptomatic COPD patients (CAT score >10)

Mean age: 69 years

Mean FEV1: 65.8% predicted

All prior users of HH-DPI for >6 months

### Methods

Open-label sequential treatment design

**Day 0-14:** Handihaler DPI (HH-DPI)  
*Low Fine-Particle Fraction (~19%)*

**Day 14-28:** Respimat SMI (RM-SMI)  
*High Fine-Particle Fraction (~65-80%)*

*Tiotropium*

<b>Patient demographics</b>
Patients (n)
Age (years)
Male (n)
BMI (kg·m <sup>-2</sup> )
Smoking (pack-years)
Exacerbations in past year (n)
mMRC dyspnoea score
CAT score
<b>Impulse oscillometry</b>
R5 (kPa·s·L <sup>-1</sup> )
R20 (kPa·s·L <sup>-1</sup> )
R5–R20 (kPa·s·L <sup>-1</sup> )
X5 (kPa·s·L <sup>-1</sup> )
AX (kPa·L <sup>-1</sup> )
<b>Multiple breath nitrogen washout</b>
S <sub>cond</sub> (L <sup>-1</sup> )
S <sub>acin</sub> (L <sup>-1</sup> )
FRC (L)
LCI2.5%
LCI5%
<b>Body plethysmography</b>
RV (L)
VC (L)
TLC (L)
FRC (L)
D <sub>LCO</sub> SB (mmol·min <sup>-1</sup> ·kPa <sup>-1</sup> )
<b>Spirometry</b>
FEV <sub>1</sub> (L)
FEV <sub>1</sub> (% predicted)
FVC (L)
FVC (% predicted)
FEV <sub>1</sub> /FVC
PEF (L·s <sup>-1</sup> )
PIF (L·s <sup>-1</sup> )
MEF <sub>75</sub> (L·s <sup>-1</sup> )
MEF <sub>50</sub> (L·s <sup>-1</sup> )
MEF <sub>25</sub> (L·s <sup>-1</sup> )
MEF <sub>25-75</sub> (L·s <sup>-1</sup> )

## Key Results: Impulse Oscillometry (Pre-dose Trough Values)

Parameter	Day 0 (Baseline) Pre-HH-DPI	Day 14 Post-14d HH-DPI / Pre-RM-SMI	Day 28 Post-14d RM-SMI
<b>R5</b> (kPa·s·L <sup>-1</sup> ) Total airway resistance	0.58 (0.29–1.10)	0.53 (0.28–1.11) ns vs Day 0	<b>0.50 (0.27–1.02) *</b>
<b>R20</b> (kPa·s·L <sup>-1</sup> ) Large airway resistance	0.37 (0.21–0.63)	0.35 (0.21–0.61)	0.34 (0.2–0.60)
<b>R5–R20</b> (kPa·s·L <sup>-1</sup> ) Small airway resistance	0.21 (0.03–0.62)	0.18 (0.03–0.52) ns vs Day 0	<b>0.16 (0.03–0.42) *</b>

\* ps0.05 (Day 28 pre-dose vs Day 14 pre-dose via Welch's t-test). Data presented as mean (range).

## Conclusions

Targeted distribution of inhaled therapy to the diseased region (small airways) achieves better physiological responses, independent of simply correcting inhaler technique.

Small airway dysfunction should be actively sought in the clinic and considered a treatable trait with targeted therapies.

# Assessment of Airway Disease

Category	Representative Techniques	Strengths	Limitations
Routine lung function	Spirometry Body plethysmography	Widely available; easy to use in clinical practice	Indirect or non-specific for small airway disease
Sensitive functional tests	Oscillometry Inert gas washout	More sensitive to early/peripheral airway dysfunction	Limited standardization and availability
Imaging	CT Hyperpolarized MRI	Visualizes spatial distribution and ventilation heterogeneity	Radiation exposure with CT; limited accessibility for MRI
Direct / invasive assessment	Histology Endobronchial OCT	Direct evaluation of small airway pathology	Invasive; not suitable for routine use