CHALLENGING SPIROMETRY

: NEW LUNG FUNCTION TEST – IOS, DLCO, RV/TLC, ETC.

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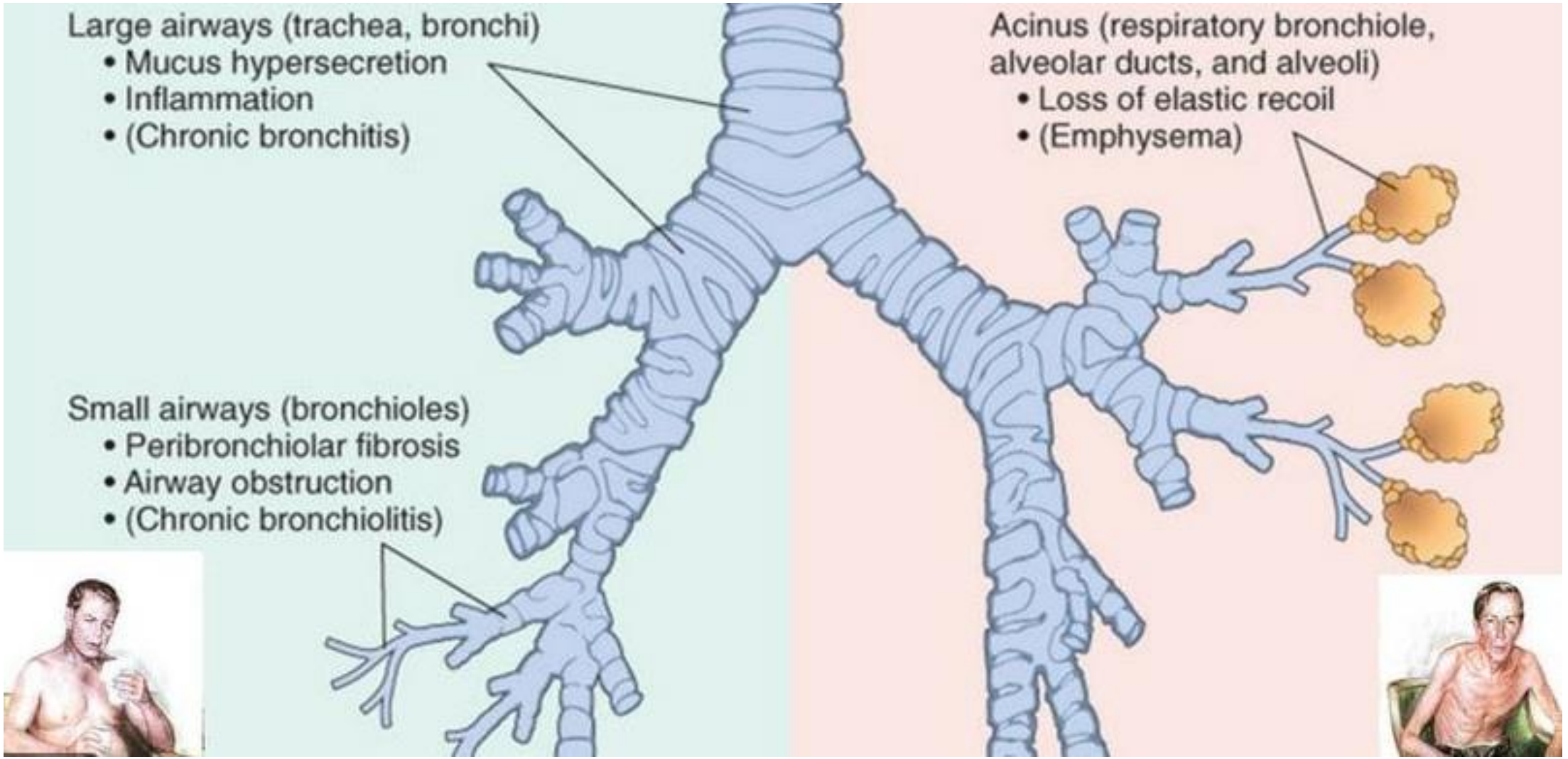
- Diagnosis of COPD by spirometry
- Concerns in assessing COPD using spirometry
- Multiple faces of COPD
- New diagnostic modalities
- Summary

Chronic bronchitis

- inflammation of large and small airway

Emphysema

- Enlargement of airspaces and destruction of lung tissue



CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

- The hallmark of COPD
  - ⇒ **Airway obstruction**
  - ⇒ Traditionally diagnosed by simple spirometry

Table 2—*Recommendations Regarding Evaluation of Patients Thought to Have "COPD"*

Minimal workup (in addition to history and physical examination):

1. Examination of the sputum
2. Spirometry before and after bronchodilator
3. Chest roentgenogram
4. Complete blood cell count and differential smear
5. Blood test for α_1-antitrypsin level
6. Baseline electrocardiogram
7. Follow-up spirometry after maximal therapy
8. Arterial blood gases if there is evidence of cor pulmonale, cyanosis, erythrocytosis, or if the FEV_1 is below 1.0 L

Helpful additional tests:

1. Pulmonary diffusing capacity
2. A small battery of allergy skin tests
3. Serum IgE level
4. More complete evaluation for right ventricular hypertrophy

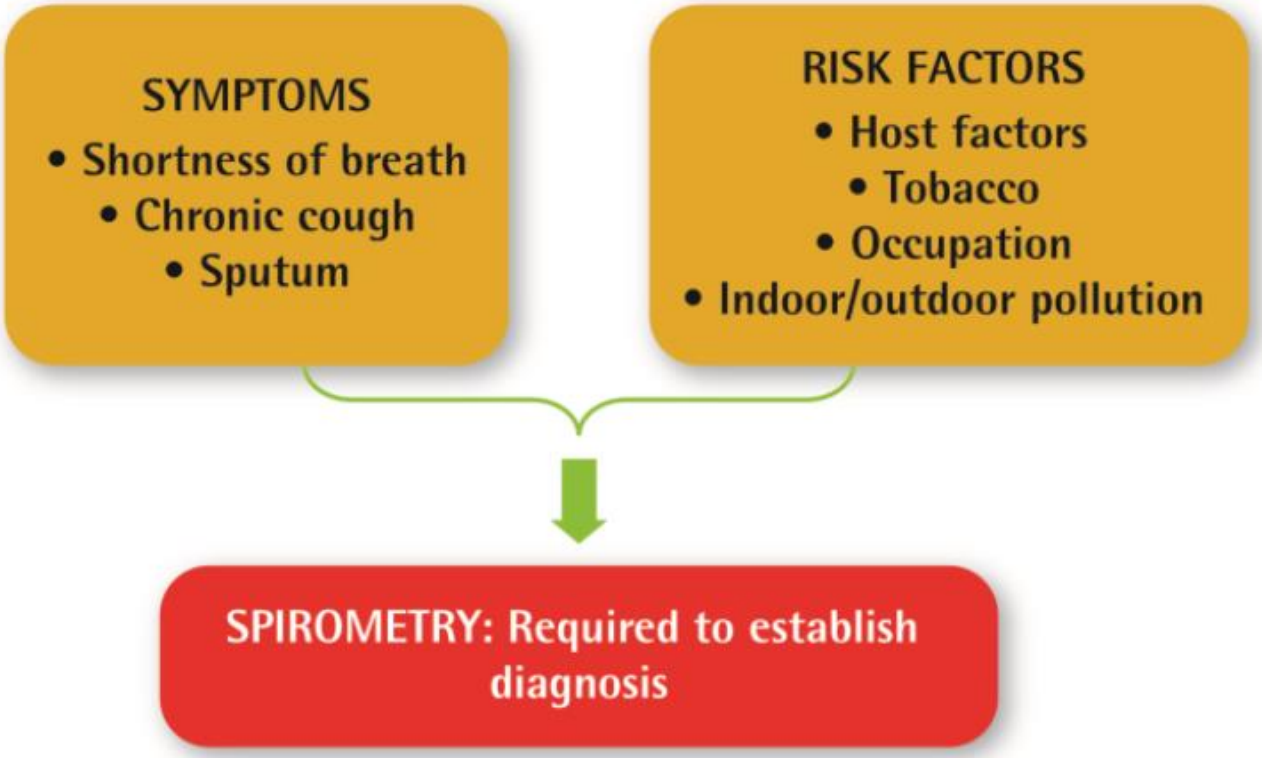
Tests of interest but rarely clinically indicated:

1. Computed tomographic scan to assess degree of emphysema
2. Cardiac catheterization to evaluate right heart and pulmonary hemodynamics
3. Esophageal balloon studies to measure lung mechanics

Burrow B. et al. Chest 1990; 97: 16-18.

DIAGNOSIS OF COPD

* **Consider** COPD if **symptoms** and/or a history of **risk factors** present
* **Confirm** the diagnosis with **spirometry** (post-bronchodilator FEV1/FVC < 0.7)



GOLD guideline 2022.

CRITERIA FOR ASSESSING COPD ACCORDING TO VARIOUS ORGANIZATIONS, LISTED BY YEAR

Organisation	Year/ Ref	Criterion
ECCS	1983[3]	FEV_1/VC or FEV_1/FVC <LLN
ATS	1987[8]	FEV_1/FVC <0.75
ATS	1991[4]	FEV_1/FVC <LLN
ECCS/ERS	1993[5]	FEV_1/VC or FEV_1/FVC <LLN
ERS	1995[7]	FEV_1/VC <88% predicted (males) or 89% (females)
BTS	1997[9]	FEV_1/FVC <0.70 and FEV_1<80% predicted
NLHEP	2000[12]	FEV_1/FVC or FEV_1/FEV_6 <LLN and FEV_1 <LLN
GOLD	2007[1]	FEV_1/FVC <0.70 post-bronchodilator
NICE	2004[10]	FEV_1/FVC <0.70 and FEV_1<80% predicted
ATS/ERS	2004[11]	FEV_1/FVC <0.70 post-bronchodilator
ATS/ERS	2005[13]	FEV_1/VC <LLN

Swanney MP et al. Thorax 2008; 63: 1046-51.

DEFINING AIRWAY OBSTRUCTION

- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defined COPD by a **fixed ratio of FEV1/FVC <0.70**, irrespective of age and gender.
- Use of **LLN (lower limit normal)** instead of the fixed FEV1/FVC ratio to detect airflow obstruction has been recommended for epidemiological studies.

  ⇒ Chances of misclassification are greater due to lack of clinical diagnosis.
- Population studies have shown that this criterion may cause falsely positive diagnosis in **elderly non-smokers**, and falsely negative diagnosis in **young smokers**, with risks of misclassification being also different in **males and females**.

Brusasco V et al. Respirology 2015; 20: 209-218.

FALSELY DIAGNOSIS IN ELDERLY NON-SMOKERS

- FEV1/FVC from 40,646 adults (including 13,136 asymptomatic never smokers) aged 17–90+ yrs. were available from American, English and Dutch population-based surveys.
- To study differences in the prevalence of airway obstruction when applying four international guidelines to three population samples
  - LLN criteria
  - GOLD criteria
  - ATS/ERS criteria
  - BTS criteria

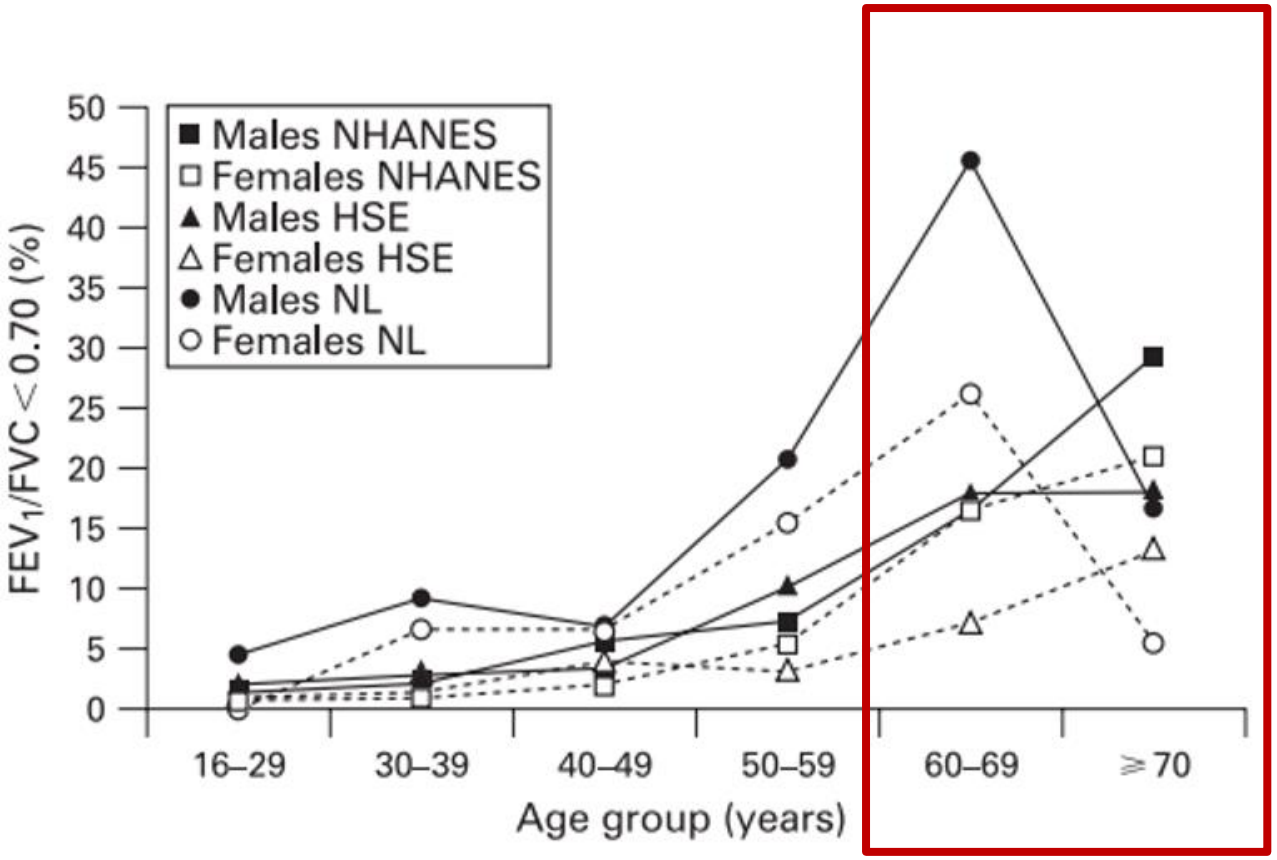


Figure. Percentages of healthy adults (asymptomatic never smokers)

Swanney MP et al. Thorax 2008; 63: 1046-51.

FALSELY DIAGNOSIS IN YOUNG SMOKERS

- **1,503 spirometry tests** from three hospitals at two academic medical centers between December 1, 2003, and February 29, 2004, were reviewed.
- Reference values from studies by Hankinson, Crapo, Knudson, and Morris.

Table 3—*Effect of Age on Discordance Comparing the Hankinson Method to the 70% Fixed Method in Diagnosing Obstruction

Age Group, yr	Patients, No.	Concordance of Hankinson and 70% Fixed Method → Agree, %	Discordance, %	
			Hankinson → No Obstruction 70% Fixed → Obstruction	Hankinson → Obstruction 70% Fixed → No Obstruction
14–31	152	91.45	0	8.55
32–41	155	92.26	0	7.74
42–46	146	95.89	0.68	3.42
47–50	156	97.42	1.28	1.28
51–54	155	99.35	0.65	0
55–58	142	95.77	4.23	0
59–63	180	90.56	9.44	0
64–67	135	91.85	8.15	0
68–73	142	86.62	13.38	0
74–95	140	83.57	16.43	0

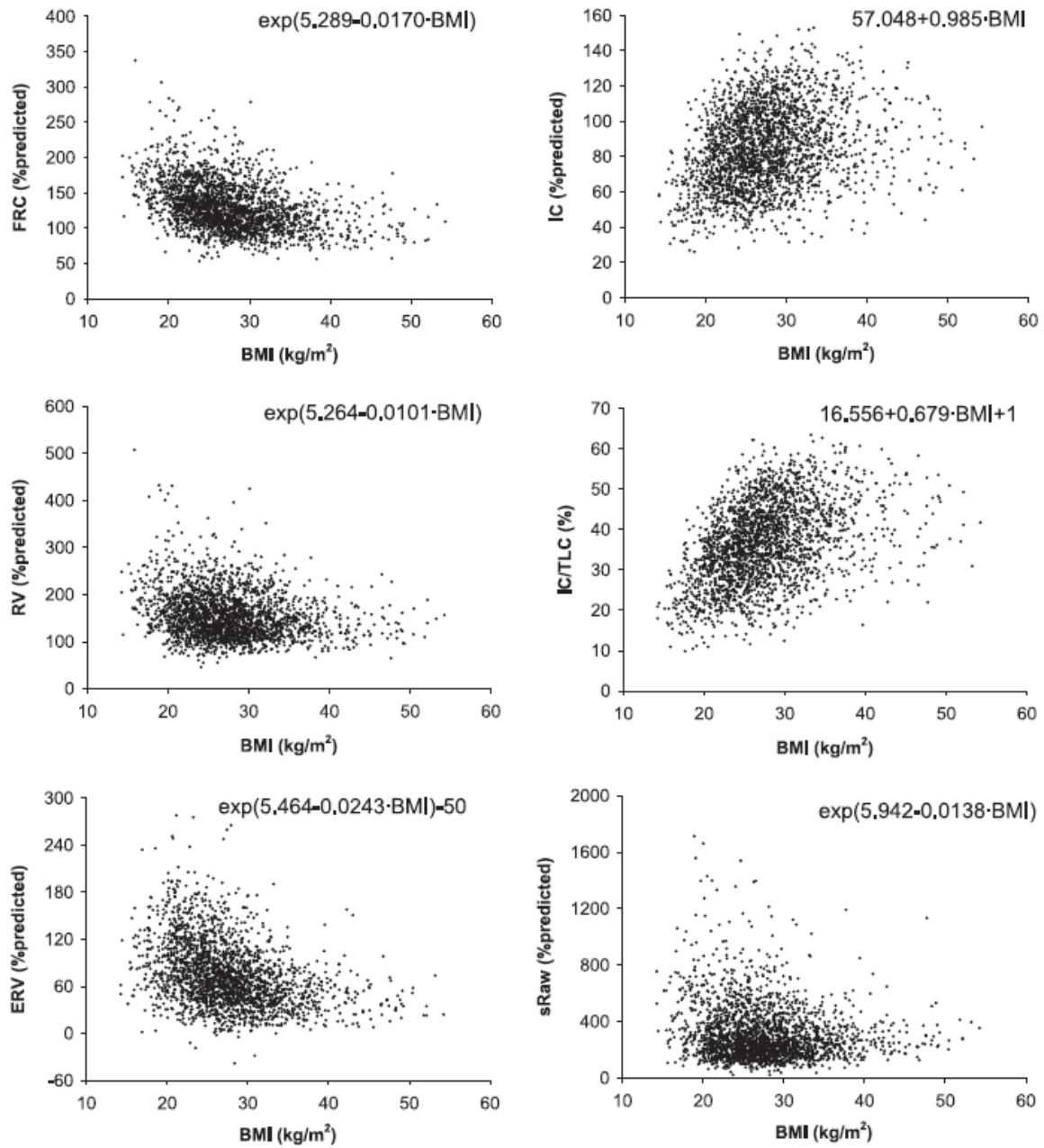
Scott D Roberts et al. Chest 2006; 130(1): 200-6.

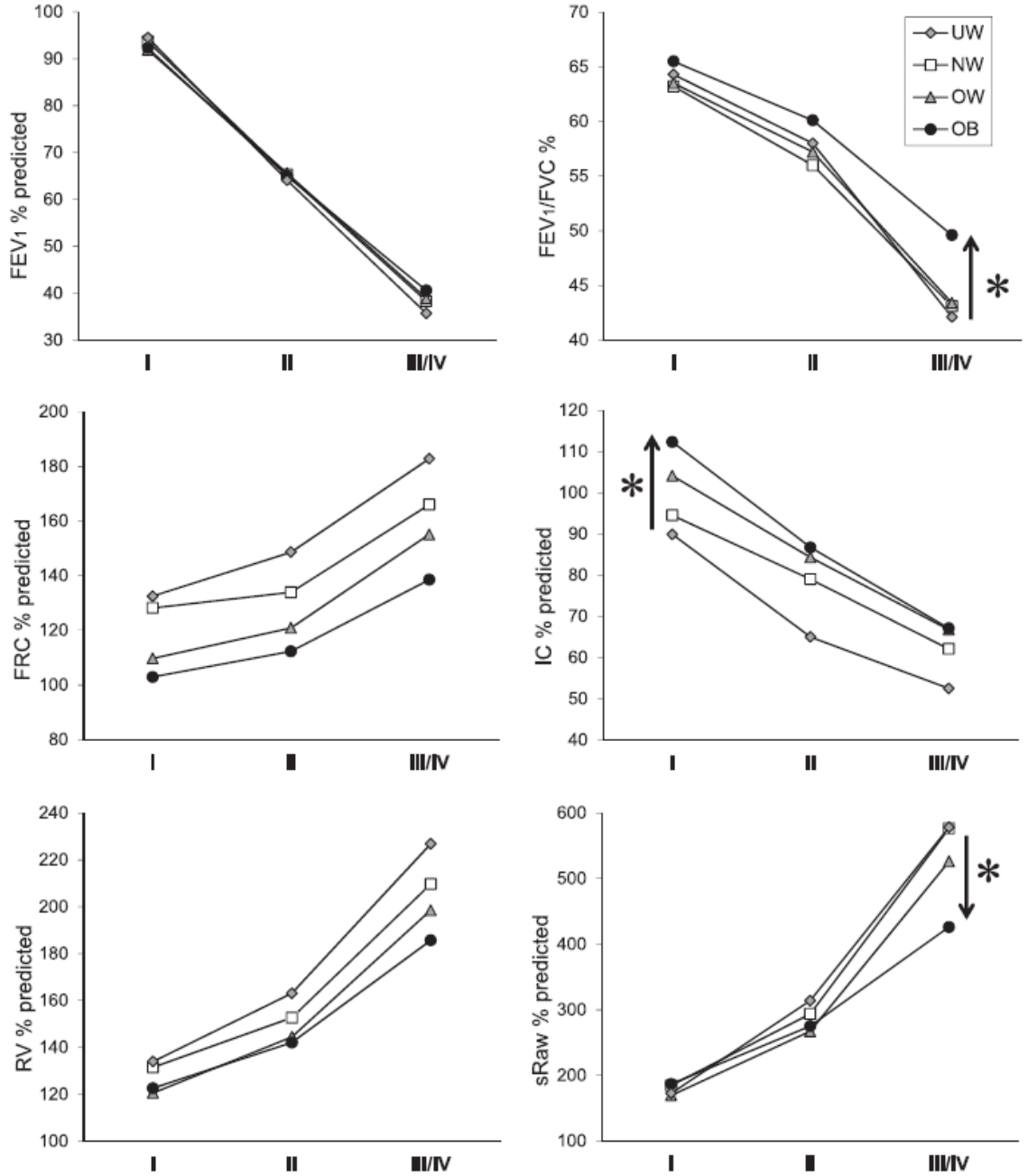
BMI ON LUNG VOLUMES IN PTS WITH AIRWAY OBSTRUCTION

- We studied the impact of increasing **BMI on static lung volumes and airway function** in a cohort of 2,265 subjects from a large pulmonary function laboratory database who were 40 to 80 years of age and met **GOLD** (Global Initiative for Chronic Obstructive Lung Disease) spirometric criteria for COPD (**postbronchodilator FEV 1 /FVC , 0.7**).
- We also evaluated the influence of severity of airway obstruction (by GOLD criteria) on these relationships.

Denis E. O'Donnell et al. Chest 2011; 140(2): 461-468.

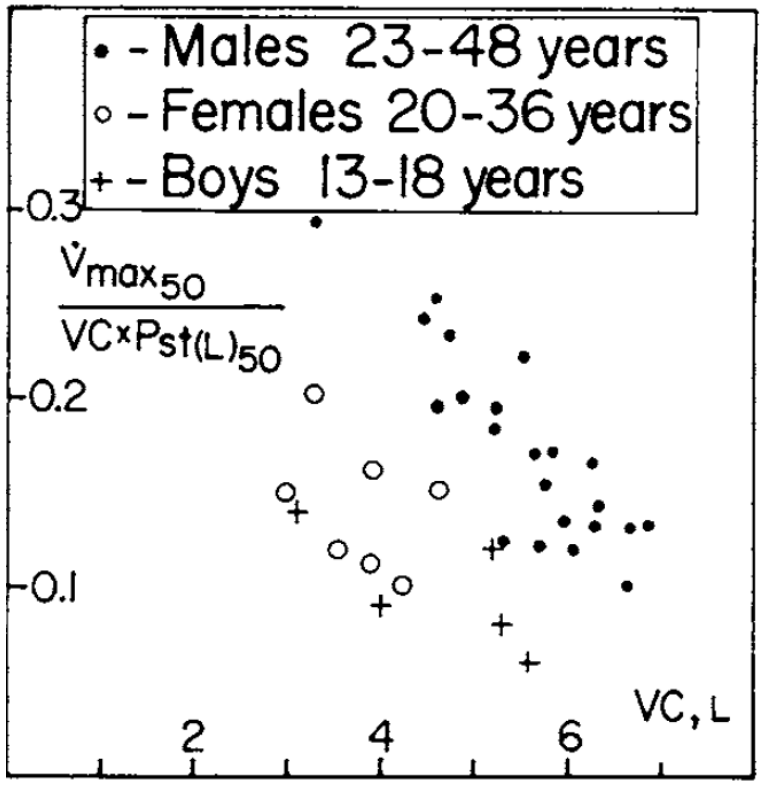
Variable	Underweight (n = 74)	Normal Weight (n = 733)	Overweight (n = 804)	Obese (n = 654)
Sex, % male	45.9	52.8	68.3	62.4
Age, y	65.0 ± 9.1	65.8 ± 9.4	65.5 ± 9.4	63.4 ± 9.5
BMI, kg/m²	17.1 ± 1.0[a]	22.4 ± 1.7	27.4 ± 1.[a]	34.8 ± 4.6[ab]
Weight, kg	46.5 ± 5.3[a]	61.7 ± 8.7	77.1 ± 9.0[a]	96.8 ± 16.0[ab]
Height, cm	164 ± 8	165 ± 9	168 ± 9	167 ± 9
GOLD stage, No. (%)				
I	8 (10.8)	186 (25.4)	231 (28.7)	195 (29.8)
II	29 (39.2)	354 (48.3)	405 (50.4)	341 (52.1)
III/IV	37 (50.0)	193 (26.3)	168 (10.9)	118 (18.0)
FEV_1/FVC postbronchodilator, %	51 ± 13[a]	54 ± 11	56 ± 10[a]	60 ± 8[ab]
FEV_1 postbronchodilator, % predicted	53 ± 22[a]	65 ± 22	68 ± 20	69 ± 20[a]
FEV_1 reversibility, L (%)	0.08 ± 0.12 (7 ± 11)	0.12 ± 0.15 (10 ± 12)	0.14 ± 0.16 (10 ± 12)	0.15 ± 0.16[a] (11 ± 13)
Prebronchodilator pulmonary function				
FEV_1, % predicted	50 ± 20[a]	61 ± 22	62 ± 21	63 ± 20
FEV_1/FVC, %	52 ± 12	55 ± 11	56 ± 10[a]	60 ± 9[ab]
FEF_{50}, % predicted	18 ± 11[a]	22 ± 14	25 ± 14[a]	27 ± 14[a]
TLC, % predicted	117 ± 15	114 ± 18	109 ± 17[a]	104 ± 16[ab]
SVC, % predicted	72 ± 18[a]	82 ± 19	82 ± 18	79 ± 18[ab]
IC, % predicted	58 ± 18[a]	74 ± 21	81 ± 22[a]	84 ± 23[ab]
IC/TLC, %	22 ± 7[a]	30 ± 8	35 ± 10[a]	37 ± 10[ab]
FRC, % predicted	165 ± 30[a]	147 ± 35	133 ± 33[a]	124 ± 32[ab]
RV, % predicted	198 ± 54[a]	174 ± 57	163 ± 53[a]	159 ± 51[a]
RV/TLC, %	63 ± 10[a]	56 ± 11	54 ± 12[a]	53 ± 11[a]
ERV, % predicted	96 ± 42	91 ± 45	71 ± 38[a]	54 ± 30[ab]
Raw, % predicted	298 ± 136	284 ± 144	281 ± 126	300 ± 122
sRaw, % predicted	505 ± 266	432 ± 283	387 ± 234[a]	379 ± 223[a]
DLCO, % predicted	70 ± 23	75 ± 25	79 ± 24[a]	77 ± 22
DLCO/VA, % predicted	73 ± 22[a]	83 ± 26	94 ± 27[a]	106 ± 26[ab]
VA, % predicted TLC	71 ± 16[a]	77 ± 16	78 ± 15	78 ± 15


exp(5.289-0.0170·BMI)
FRC (%predicted)
BMI (kg/m²)
57.048+0.985·BMI
IC (%predicted)
BMI (kg/m²)
exp(5.264-0.0101·BMI)
RV (%predicted)
BMI (kg/m²)
16.556+0.679·BMI+1
IC/TLC (%)
BMI (kg/m²)
exp(5.464-0.0243·BMI)-50
ERV (%predicted)
BMI (kg/m²)
exp(5.942-0.0138·BMI)
sRaw (%predicted)
BMI (kg/m²)


FEV1 % predicted
100
90
80
70
60
50
40
30
I
II
III/IV
FEV1/FVC %
70
65
60
55
50
45
40
UW
NW
OW
OB
*
FRC % predicted
200
180
160
140
120
100
80
IC % predicted
120
110
100
90
80
70
60
50
40
RV % predicted
240
220
200
180
160
140
120
100
sRaw % predicted
600
500
400
300
200
100

DYSANAPSIS IN NORMAL LUNGS

- Airway size (maximal expiratory flow/static recoil pressure at 50% of VC)
- Lung size (vital capacity)



- Bear in mind the different implications of lung size and lung inflation to airway conductance.
- FEV1 and lung volumes are determined by overall lung elastic recoil.

Mead J. Am. Rev. Respir. Dis. 1980; 121: 339-42.

MISMATCH OF AIRWAY TREE CALIBER TO LUNG SIZE BY CT

- A retrospective cohort study of 2 community-based samples

  - MESA Lung Study : 2531 participants (6 US sites, 2010-2018)

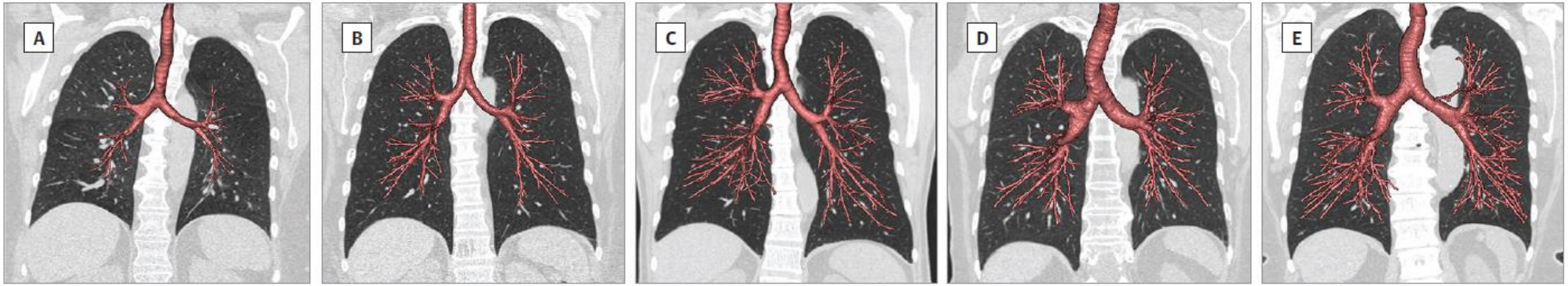
  - CanCOLD study : 1272 participants (9 Canadian sites, 2010-2018), and a

  - SPIROMICS study: 2726 participants (12 US sites, 2011-2016)

- To determine whether **dysanapsis**, a mismatch of airway tree caliber to lung size, assessed by computed tomography (CT), is associated with incident COPD among older adults and lung function decline in COPD.

Benjamin M. Smith et al. JAMA 2020; 323(22): 2268-2280.

Participant characteristics at baseline	No. (%) of participants		
	Community-based studies		
	MESA Lung [a] (n=2531)	CanCOLD[b] (n=1272)	SPIROMICS case-control study[c] (n=2726)
FEV_1, mean (SD), L	2.3 (0.7)	2.6 (0.8)	1.9 (0.9)
Predicted FEV_1, mean (SD), %	96 (19)	94 (20)	66 (27)
FEV_1:FVC, mean (SD)	0.74 (0.08)	0.71 (0.08)	0.58 (0.16)
CT total lung volume, mean (SD), L	4.8 (1.3)	5.3 (1.3)	5.9 (1.5)
Prevalent COPD[f]	96 (4.4)	171 (13.4)	1577 (57.9)
Total No.	2170		
Emphysema, median (IQR), % [g]	1.4 (0.6-3.0)	2.3 (1.1-4.2)	3.2 (1.0-10.8)
Quantitative measures of dysanapsis			
Airway to lung ratio, mean (SD)[h]	0.033 (0.004)	0.032 (0.003)	0.032 (0.004)
Predicted airway tree size, mean (SD), %[i]	98.3 (10.4)	95.7 (9.3)	98.0 (11.1)
Follow-up spirometry analysis after baseline airway to lung ratio assessment			
No. of participants	1458	1032	2139
Total follow-up interval, median (IQR), y	6.2 (5.8-6.6)	3.1 (2.9-3.3)	2.1 (1.1-3.0)
No. of follow-up spirometry assessments, median (IQR)	1 (1-1)	2 (2-2)	2 (1-3)
Change in FEV_1:FVC, mean (SD), per 5 y	−0.01 (0.05)	−0.01 (0.09)	−0.04 (0.15)
Change in FEV_1, mean (SD), mL/y	−32 (40)	−36 (75)	−47 (14)
Follow-up incident COPD analysis after baseline airway to lung ratio assessment			
No. with incident COPD/No. without prevalent COPD (%)	31/1110 (2.8)	113/752 (15.0)	237/933 (25.4)
Total follow-up interval, median (IQR), y	6.2 (5.8-6.6)	3.1 (3.0-3.3)	2.1 (1.5-3.0)

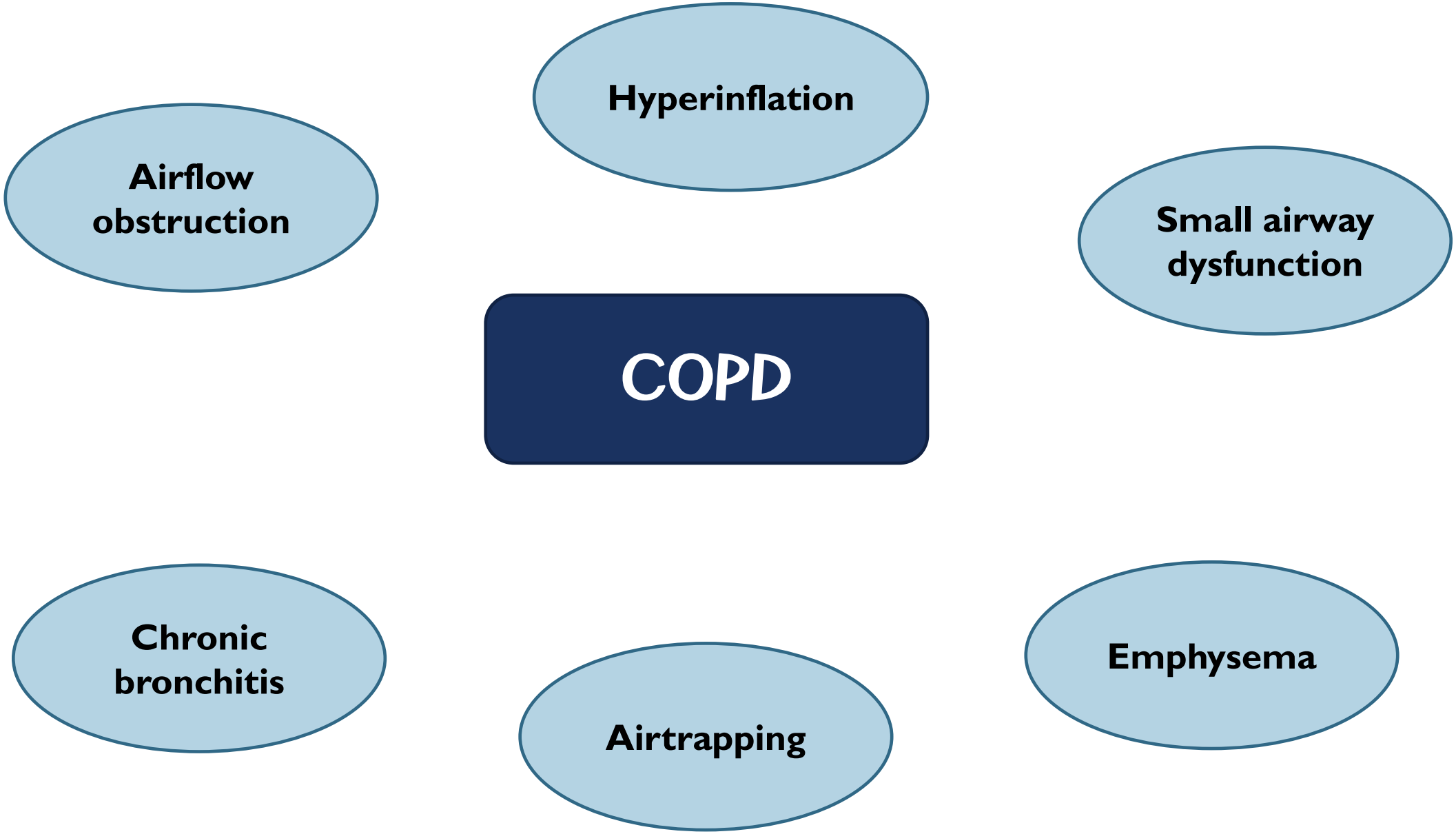


78%	91%	100%	105%	120%
FEV1/FVC 0.55	FEV1/FVC 0.68	FEV1/FVC 0.80	FEV1/FVC 0.81	FEV1/FVC 0.91

Benjamin M. Smith et al. JAMA 2020; 323(22): 2268-2280.

Table 3. Baseline FEV_1:FVC Variation Statistically Accounted for, and Incident COPD C Statistic and NRI Increment With Standard COPD Risk Factors and Airway to Lung Ratio in the Community-Based Studies

	MESA Lung	CanCOLD
Baseline FEV_1:FVC, No.	2531	1272
Increment in proportion of baseline FEV_1:FVC % statistically accounted for, (95% CI)[a,b]		
Age, age × age, sex, height, height × height, and race/ethnicity	14.4 (14.2-14.5)	3.4 (3.3-3.5)
Primary tobacco smoke exposures	4.7 (4.6-4.8)	4.4 (4.3-4.5)
Secondhand smoke, occupational or environmental pollutants, and asthma	2.9 (2.8-3.0)	3.9 (3.9-4.0)
Airway to lung ratio	16.7 (16.6-16.9)	18.5 (18.2-18.8)
No. with incident COPD/No. without prevalent COPD (%)	98/2294 (4.3)	113/752 (15.0)
Cumulative C statistic for incident COPD for risk factors and airway to lung ratio, (95% CI)[b,c]		
Age, age × age, sex, height, height × height, and race/ethnicity	0.67 (0.66-0.67)	0.59 (0.58-0.59)
Primary tobacco smoke exposures	0.71 (0.71-0.72)	0.67 (0.67-0.67)
Secondhand smoke, occupational or environmental pollutants, and asthma	0.76 (0.76-0.77)	0.70 (0.70-0.71)
Airway to lung ratio	0.83 (0.82-0.83)	0.74 (0.74-0.75)
NRI improvement for incident COPD for risk factors and airway to lung ratio, (95% CI)[b,d]		
Age, age × age, sex, height, height × height, and race/ethnicity	0.58 (0.56-0.61)	0.31 (0.28-0.33)
Primary tobacco smoke exposures	0.37 (0.34-0.40)	0.41 (0.39-0.43)
Secondhand smoke, occupational or environmental pollutants, and asthma	0.37 (0.34-0.40)	0.28 (0.25-0.31)
Airway to lung ratio	0.60 (0.57-0.62)	0.50 (0.47-0.53)


Hyperinflation
Airflow obstruction
Small airway dysfunction
COPD
Chronic bronchitis
Airtrapping
Emphysema

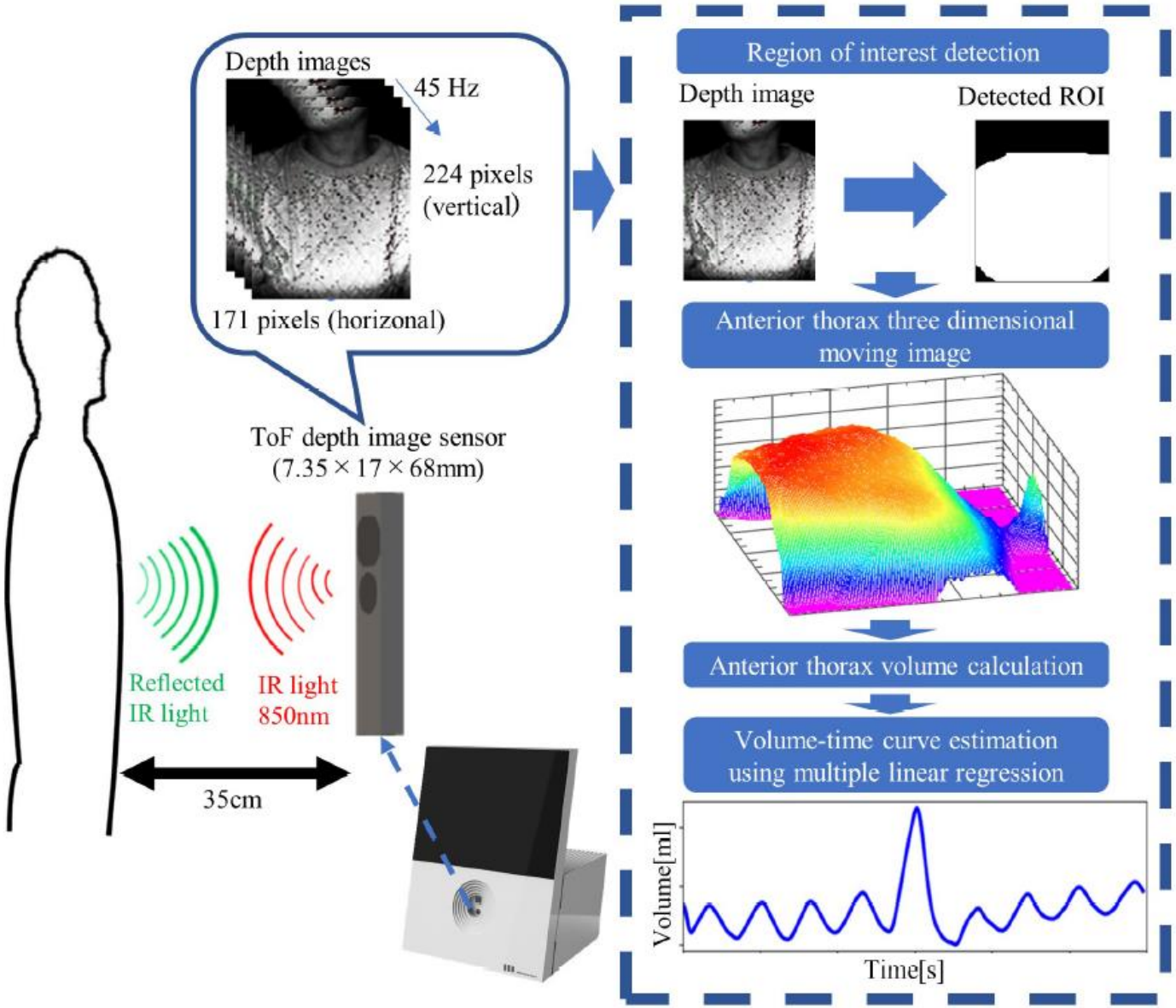
NEWLY APPROACHED METHOD IN COPD

- Infrared time-of-flight depth image sensor to detect early airflow limitation
- RV/TLC ratio
- DLCO (diffusing capacity of the lung for carbon monoxide), KCO or DLCO/VA
- Measures of airway resistance (Raw) using body plethysmography
- Total respiratory system resistance (Rrs) using the forced oscillation technique (FOT) or impulse oscillometry (IOS)

NOVEL EARLY AIRFLOW LIMITATION SCREENING SYSTEM

- Developed a novel non-contact early airflow limitation screening system (**EAFL-SS**) that does not require calibration to the individual by a spirometer at home.
- The system is based on an infrared time-of-flight (ToF) depth image sensor, which is integrated into several smartphones for photography focusing or augmented reality.

Hiroki Takamoto et al. Front. Physiol. 11; 552942.



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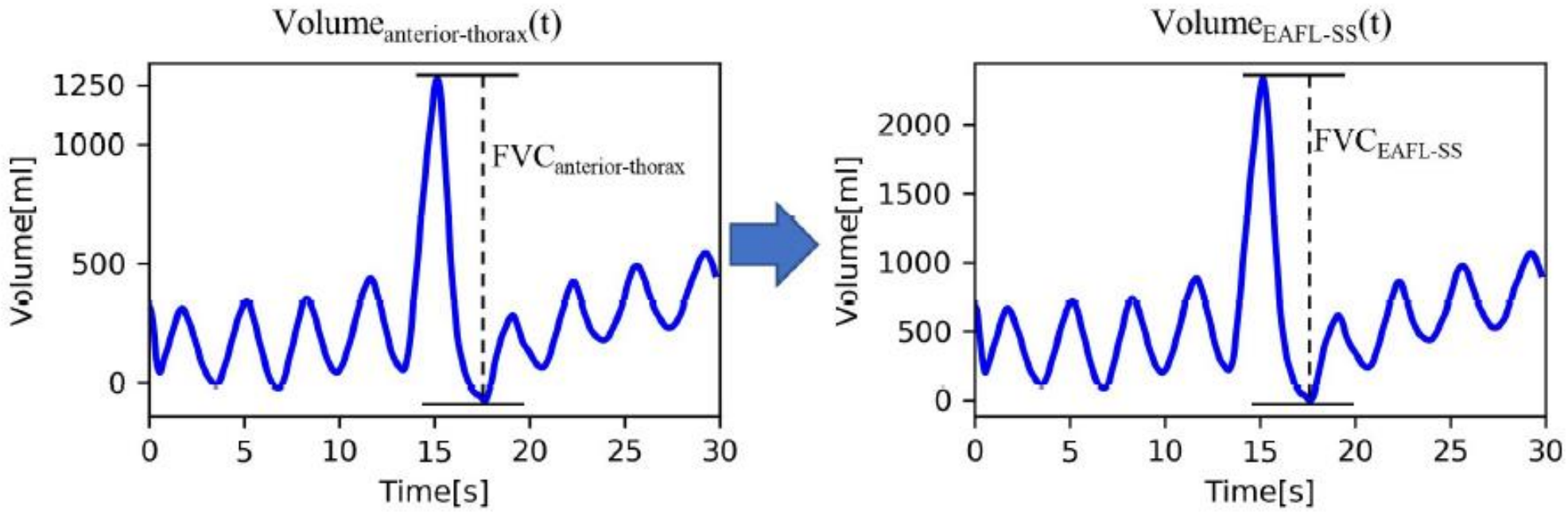

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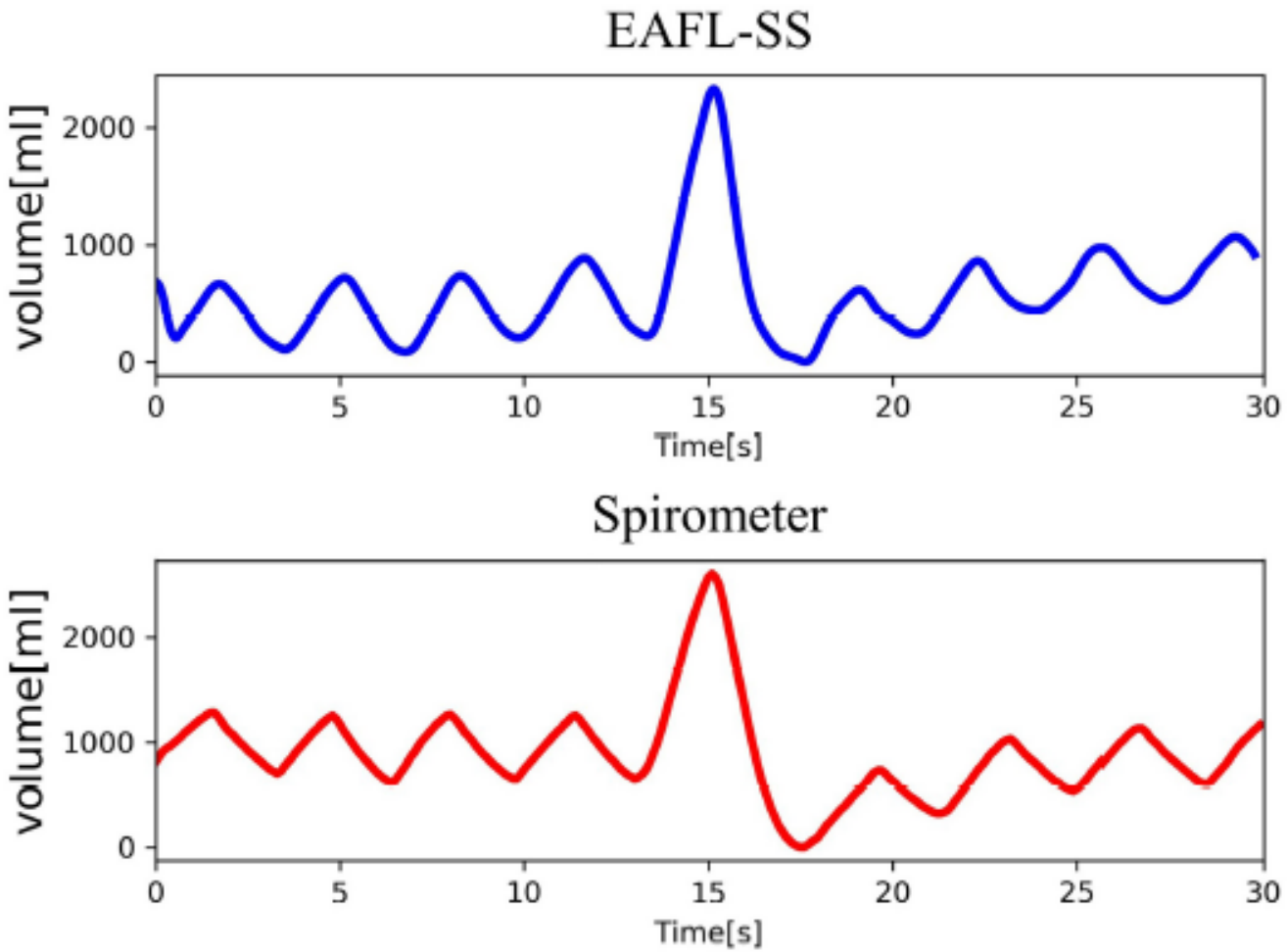
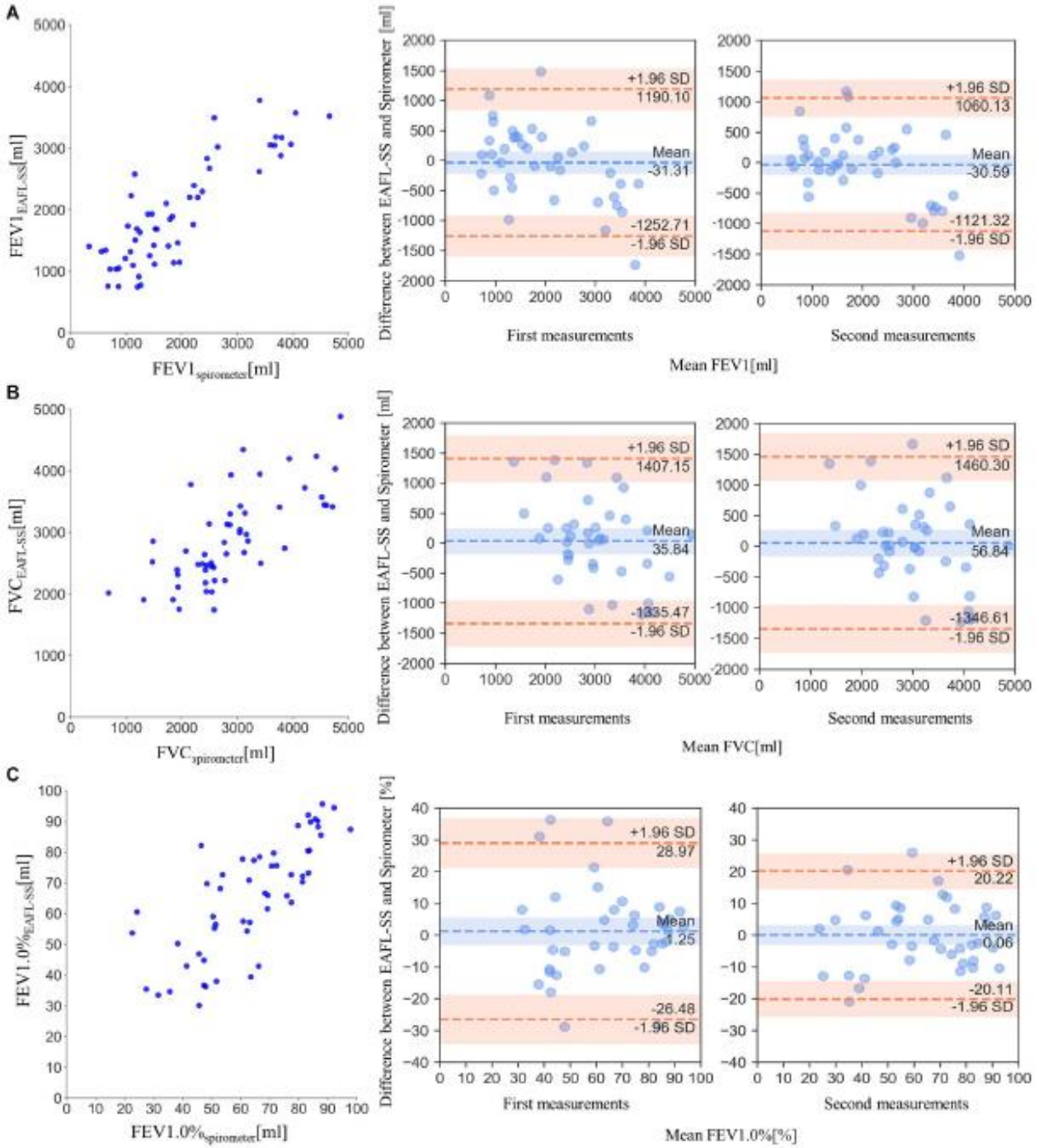
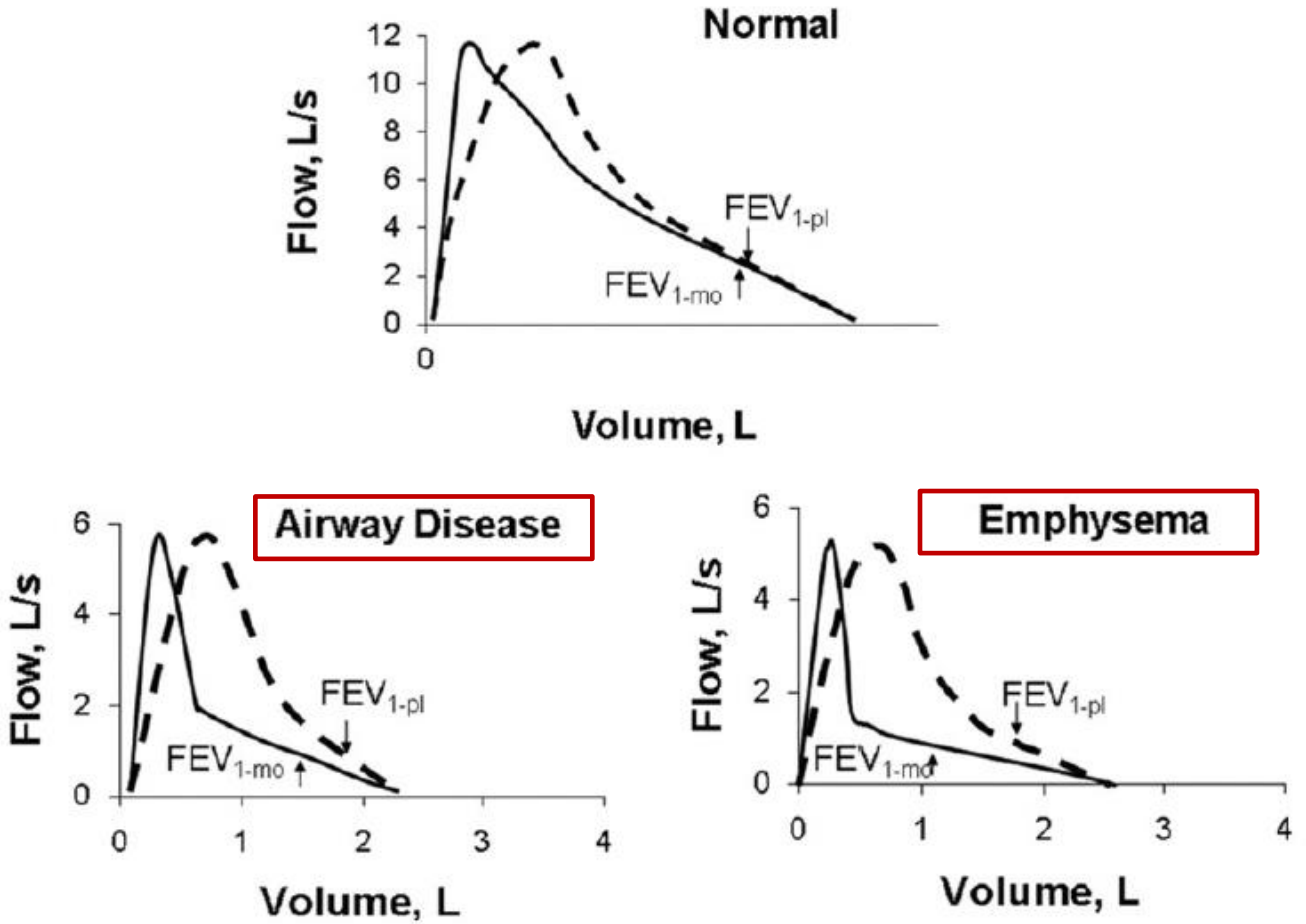


Hiroki Takamoto et al. Front. Physiol. 11; 552942.


A
FEV1EAFL-SS[ml]
FEV1spirometer[ml]
Difference between EAFL-SS and Spirometer [ml]
+1.96 SD
1190.10
Mean
-31.31
-1252.71
-1.96 SD
First measurements
+1.96 SD
1060.13
Mean
-30.59
-1121.32
-1.96 SD
Second measurements
Mean FEV1[ml]
B
FVCEAFL-SS[ml]
FVCspirometer[ml]
Difference between EAFL-SS and Spirometer [ml]
+1.96 SD
1407.15
Mean
35.84
-1335.47
-1.96 SD
First measurements
+1.96 SD
1460.30
Mean
56.84
-1346.61
-1.96 SD
Second measurements
Mean FVC[ml]
C
FEV1.0%EAFL-SS[ml]
FEV1.0%spirometer[ml]
Difference between EAFL-SS and Spirometer [%]
+1.96 SD
28.97
Mean
1.25
-26.48
-1.96 SD
First measurements
+1.96 SD
20.22
Mean
0.06
-20.11
-1.96 SD
Second measurements
Mean FEV1.0%[%]

THORACIC GAS VOLUME (TGV) IN COPD



Respirology Case Reports 2014; 2(4): 141-143.

RV/TLC

- Air trapping, measured as an increase in residual volume (RV) relative to the total lung capacity (RV/TLC), is one of the earliest physiological manifestations of COPD.
- Increased RV/TLC contributes to hyperinflation, which is a strong determinant of exercise limitation and the sensation of exertional dyspnea.

LONG-TERM CHANGE IN AIR TRAPPING IN KOLD COHORT

- COPD patients from KOLD cohort, from 2005.06 to 2015.10
- RV/TLC ≥ 40%: abnormal

  RV/TLC < 40%: normal
- According to the pattern of change in the RV/TLC, patients were categorized into four groups.

  - normal -> normal: N= 76
  - abnormal -> normal: N=34
  - normal -> abnormal: N=33
  - abnormal -> abnormal: N=136

JU Lim et al. Korean J Intern Med 2021; 36(3): 636-646.

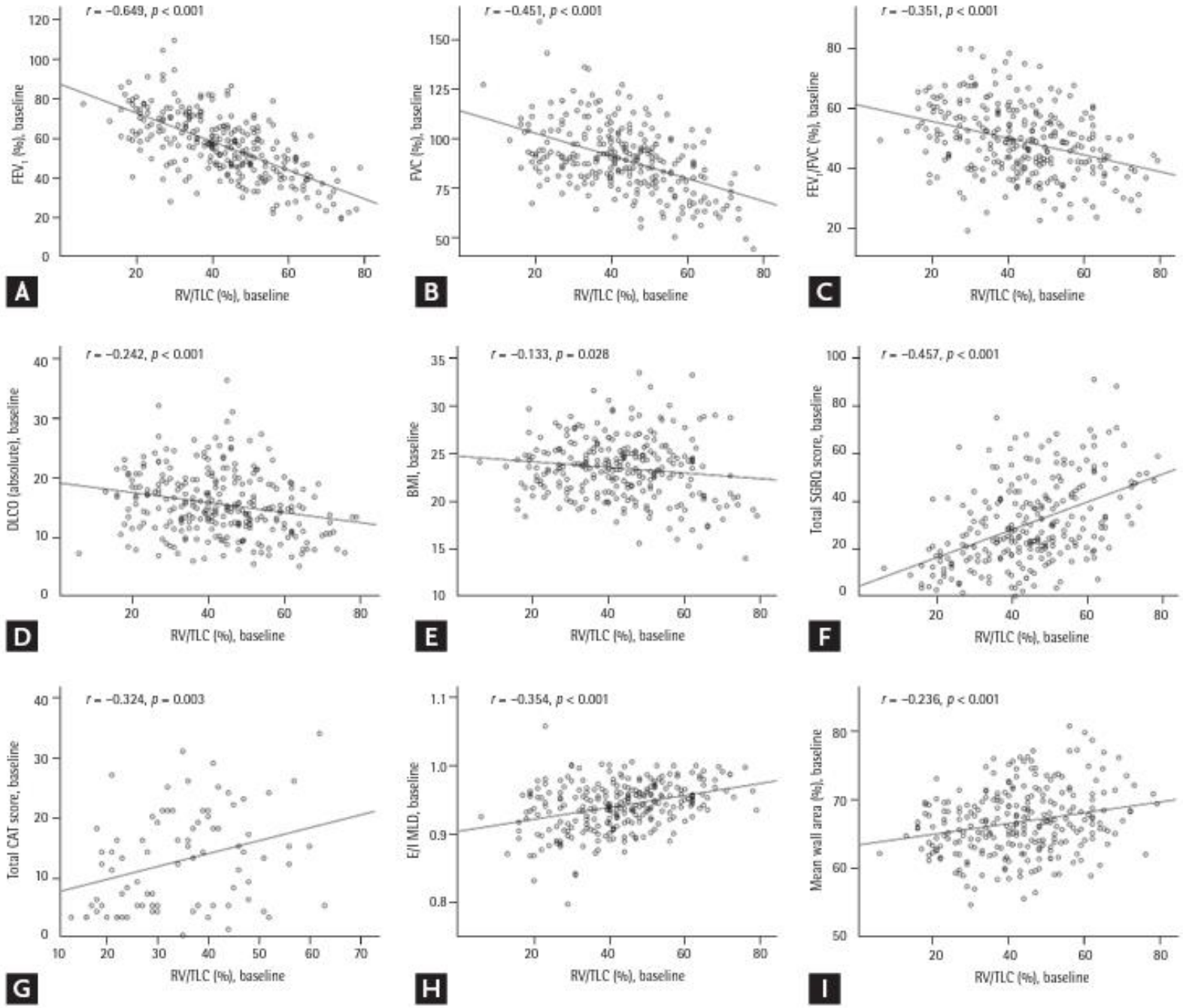

r = −0.649, p < 0.001
FEV1 (%), baseline
RV/TLC (%), baseline
A
r = −0.451, p < 0.001
FVC (%), baseline
RV/TLC (%), baseline
B
r = −0.351, p < 0.001
FEV1/FVC (%), baseline
RV/TLC (%), baseline
C
r = −0.242, p < 0.001
DLCO (absolute), baseline
RV/TLC (%), baseline
D
r = −0.133, p = 0.028
BMI, baseline
RV/TLC (%), baseline
E
r = −0.457, p < 0.001
Total SGRQ score, baseline
RV/TLC (%), baseline
F
r = −0.324, p = 0.003
Total CAT score, baseline
RV/TLC (%), baseline
G
r = −0.354, p < 0.001
E/I MLD, baseline
RV/TLC (%), baseline
H
r = −0.236, p < 0.001
Mean wall area (%), baseline
RV/TLC (%), baseline
I

Table 3. Univariate and multivariate analyses on the associations of factors with exacerbation frequency during the first year of follow-up

Characteristic	Univariate			Multivariable		
	IRR	95% CI	*p* value	IRR	95% CI	*p* value
Age[a]	0.999	0.972–1.027	0.999			
Male sex	0.950	0.451–1.999	0.892			
FEV_1 (% predicted)[a]	0.978	0.966–0.990	< 0.001	0.989	0.974–1.004	0.149
Initial SGRQ score[a]	1.027	1.015–1.038	< 0.001	1.022	1.009–1.034	0.001
Body mass index[a]	0.947	0.891–1.006	0.080			
Smoking experience	0.474	0.192–1.169	0.105			
Bronchodilator use	5.112	0.610–42.839	0.133			
Major comorbidities	1.128	0.753–1.689	0.558			
Past tuberculosis	0.858	0.533–1.379	0.526			
COPD phenotypes according to RV/TLC changes						
Normal to normal	1		0.001	1		0.794
Abnormal to normal	1.989	0.975–4.058	0.059	1.389	0.659–2.931	0.388
Normal to abnormal	1.515	0.653–3.516	0.333	1.460	0.600–3.515	0.398
Abnormal to abnormal	2.291	1.310–4.005	0.004	1.266	0.653–2.455	0.484

JU Lim et al. Korean J Intern Med 2021; 36(3): 636-646.

AIR TRAPPING AND RISK OF COPD EXACERBATION FROM KOCOSS

- Of 2,181 participants, 902 patients measured the RV/TLC ratio in the baseline enrollment, and 410 were evaluated for assessing the development of COPD exacerbation.
- To evaluate air trapping, we identified the ratio of residual volume (RV) to total lung capacity (TLC) of patients with COPD from the Korean COPD Subgroup Study (KOCOSS) cohort.
- To investigate the impact of air trapping as a continuous parameter on development of COPD exacerbation during 3 years of follow-up.

Y Kim, SH Kim, et al.Front. Med. 9; 835069.

TABLE 1 | Baseline characteristics of the study population.

	RV/TLC ratio quartiles				
	Q1: < 34% (*n* = 218)	**Q2: 34–40% (*n* = 223)**	**Q3: 41–48% (*n* = 223)**	**Q4: ≥ 49% (*n* = 238)**	**P_{trend}**
Age (years)	67.0 (60.0–73.0)	68.0 (63.0–73.0)	71.0 (66.0–75.0)*†	72.0 (66.0–76.0)*†	<0.001
Male	208 (95.4)	217 (97.3)	218 (97.8)	229 (96.2)	0.620
BMI (kg/m^2) (*n* = 899)	23.6 (22.1–25.8)	23.4 (21.8–25.7)	22.7 (20.7–25.2)*†	22.2 (19.9–24.7)*†‡	<0.001
College graduate (*n* = 897)	36 (16.8)	30 (13.5)	20 (9.0)*	23 (9.7)*	0.009
Occupational exposure (*n* = 885)	77 (36.5)	96 (44.0)	87 (39.7)	99 (41.8)	0.447
Smoking history					
Past smoker	148 (67.9)	151 (67.7)	152 (68.2)	178 (74.8)	0.127
Current smoker	70 (32.1)	72 (32.3)	71 (31.8)	60 (25.2)	0.113
Smoking amount (pack-years)	40.0 (28.0–52.0)	40.0 (26.5–51.5)	44.0 (30.0–52.0)	42.0 (26.0–55.0)	0.308
Symptom assessment					
mMRC ≥ 2 (*n* = 900)	48 (22.0)	71 (31.8)*	71 (31.8)*	127 (53.8)*†‡	<0.001
CAT score ≥ 10	141 (64.7)	157 (70.4)	153 (68.6)	199 (83.6)*†‡	<0.001
Acute exacerbation over 3 years					
Moderate to severe exacerbation	40 (54.1)	63 (60.0)	77 (68.1)	128 (81.5)*†‡	<0.001
Severe exacerbation	10 (13.5)	12 (11.4)	30 (26.5)†	57 (36.3)*†	<0.001
Lung function					
FVC (L)	3.8 (3.3–4.2)	3.5 (3.2–3.9)*	3.2 (2.9–3.5)*†	2.6 (2.3–2.9)*†‡	<0.001
FVC (%-predicted) (*n* = 899)	91.4 (82.1–99.5)	83.5 (75.5–92.2)*	77.1 (70.9–85.0)*†	65.1 (57.4–72.9)*†‡	<0.001
FEV_1 (L)	2.2 (1.8–2.5)	1.9 (1.6–2.1)*	1.6 (1.3–1.9)*†	1.1 (0.9–1.4)*†‡	<0.001
FEV_1 (%-predicted) (*n* = 901)	73.9 (61.5–83.6)	63.2 (52.3–71.9)*	55.2 (46.6–64.6)*†	40.7 (31.8–51.1)*†‡	<0.001
FEV_1/FVC (%)	59.0 (51.0–64.0)	55.0 (46.0–63.0)*	51.0 (41.5–59.0)*†	44.5 (35.0–54.0)*†‡	<0.001
DL_{CO} (%-predicted) (*n* = 882)	67.1 (53.8–78.8)	65.8 (54.0–78.5)	62.9 (50.8–74.5)*	57.0 (46.1–68.3)*†‡	<0.001

Y Kim, SH Kim, et al.Front. Med. 9; 835069.

TABLE 3 | The RV/TLC ratio and the risk of COPD exacerbation.

	Moderate to severe exacerbation		Severe exacerbation	
***N* = 410**	**Unadjusted OR (95% CI, *p*)**	**Adjusted OR (95% CI, *p*)**	**Unadjusted OR (95% CI, *p*)**	**Adjusted OR (95% CI, *p*)**
RV/TLC ratio				
Per 10% increase	**1.63 (1.47–2.01, <0.001)**	**1.35 (1.06–1.74, 0.017)**	**1.62 (1.32–2.00, <0.001)**	**1.36 (1.05–1.75, 0.019)**
RV/TLC ratio quartiles				
1Q: <34%	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
2Q: 35–40%	1.44 (0.76–2.77, 0.266)	1.20 (0.60–2.44, 0.604)	0.80 (0.32–2.05, 0.643)	0.67 (0.25–1.85, 0.436)
3Q: 41–48%	1.82 (0.97–3.46, 0.064)	1.32 (0.64–2.75, 0.449)	2.10 (0.97–4.87, 0.069)	1.72 (0.70–4.44, 0.243)
4Q: ≥49%	**3.87 (2.05–7.40, <0.001)**	2.18 (0.99–4.86, 0.054)	**3.49 (1.71–7.76, 0.001)**	2.18 (0.88–5.73, 0.102)

Y Kim, SH Kim, et al.Front. Med. 9; 835069.

TABLE 2 | Incidence of COPD exacerbation during three years according to the percent-predicted FEV_1 and the RV/TLC ratio.

N = 410	Moderate to severe exacerbation			
	FEV_1: < 44%-pred (n = 122)	**FEV_1: 44–56% (n = 121)**	**FEV_1: 56–69% (n = 102)**	**FEV_1: ≥70% (n = 65)**
RV/TLC ratio : ≥ 49% (n = 150)	84/94 (89.4)	25/37 (67.6)	11/14 (78.6)	4/5 (80.0)
RV/TLC ratio : 41–48% (n = 104)	17/19 (89.5)	29/41 (70.7)	23/36 (63.9)	3/8 (37.5)
RV/TLC ratio : 34–40% (n = 89)	5/7 (71.4)	21/33 (63.6)	22/34 (64.7)	9/15 (60.0)
RV/TLC ratio : < 34% (n = 67)	2/2 (100)	7/10 (70.0)	8/18 (44.4)	20/37 (54.1)
Severe exacerbation				
RV/TLC ratio : ≥ 49% (n = 150)	40/94 (42.6)	11/37 (29.7)	5/14 (35.7)	1/5 (20.0)
RV/TLC ratio : 41–48% (n = 104)	7/19 (36.8)	14/41 (34.1)	6/36 (16.7)	1/8 (12.5)
RV/TLC ratio : 34–40% (n = 89)	1/7 (14.3)	4/33 (12.1)	6/34 (17.6)	0/15 (0)
RV/TLC ratio : < 34% (n = 67)	0/2 (0)	4/10 (40.0)	2/18 (11.1)	4/37 (10.8)

Data are expressed as the events/patients (percentages).
Darker shades indicate higher rates of COPD exacerbation.
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; RV, residual volume; TLC, total lung capacity.

Y Kim, SH Kim, et al.Front. Med. 9; 835069.

LUNG FUNCTION TESTING: WHEN EVERYTHING IS NOT SO SIMPLE

- 70-year-old Caucasian man, markedly overweight (BMI: 29.3 kg/m^2) and with concomitant arterial hypertension and coronary artery disease, presented with dyspnea on exertion progressing over the last year.
- He had a 60-pack-year history of cigarette smoking, which he had quit for five years.
- He was a shipping agent at a harbor with indirect exposure to asbestos for his whole occupational life.

Table 1. Post-bronchodilator lung function data.

	Measured	*z*-score
FVC (L)	3.14	–0.19
FEV_1 (L)	2.06	–1.06
FEV_1/FVC	0.66	–1.42
TLC (L)	4.48	–1.61
$\bar{R}_{insp\,5}$ ($cmH_2O \cdot s \cdot L^{-1}$)	2.31	0.02
DL_{NO} ($mL \cdot min^{-1} \cdot mmHg^{-1}$)	40.7	–7.11
DL_{CO} ($mL \cdot min^{-1} \cdot mmHg^{-1}$)	11.5	–3.58

Respirology Case Reports 2014; 2(4): 141-143.

DIFFUSING CAPACITY OF THE LUNG FOR CARDON MONOXIDE

- **The diffusing capacity of the lung for carbon monoxide (DLCO)** is a measure of gas transfer that reflects the complex interactions at the alveolar capillary interface.
- It has been strongly associated with decline in lung function and is one of the best correlates of emphysema in COPD.

S.Kakavas et al. npj Primary Care Respiratory Medicine 2021; 31: 23.
Aparna Balasubramanian et al. Chest 2019; 156(6): 1111-1119.

DLCO IN ASSESSMENT OF COPD

- Data for 1,806 participants with COPDGene study 5-year visit were analyzed, including pulmonary function testing, quality of life, symptoms, exercise performance, and exacerbation rates.
- DLCO percent predicted was primarily analyzed as a continuous variable and additionally categorized into four groups.

  (1) DLCO and FEV1>50% (reference)

  (2) only DLCO ≤50%

  (3) only FEV1≤50%

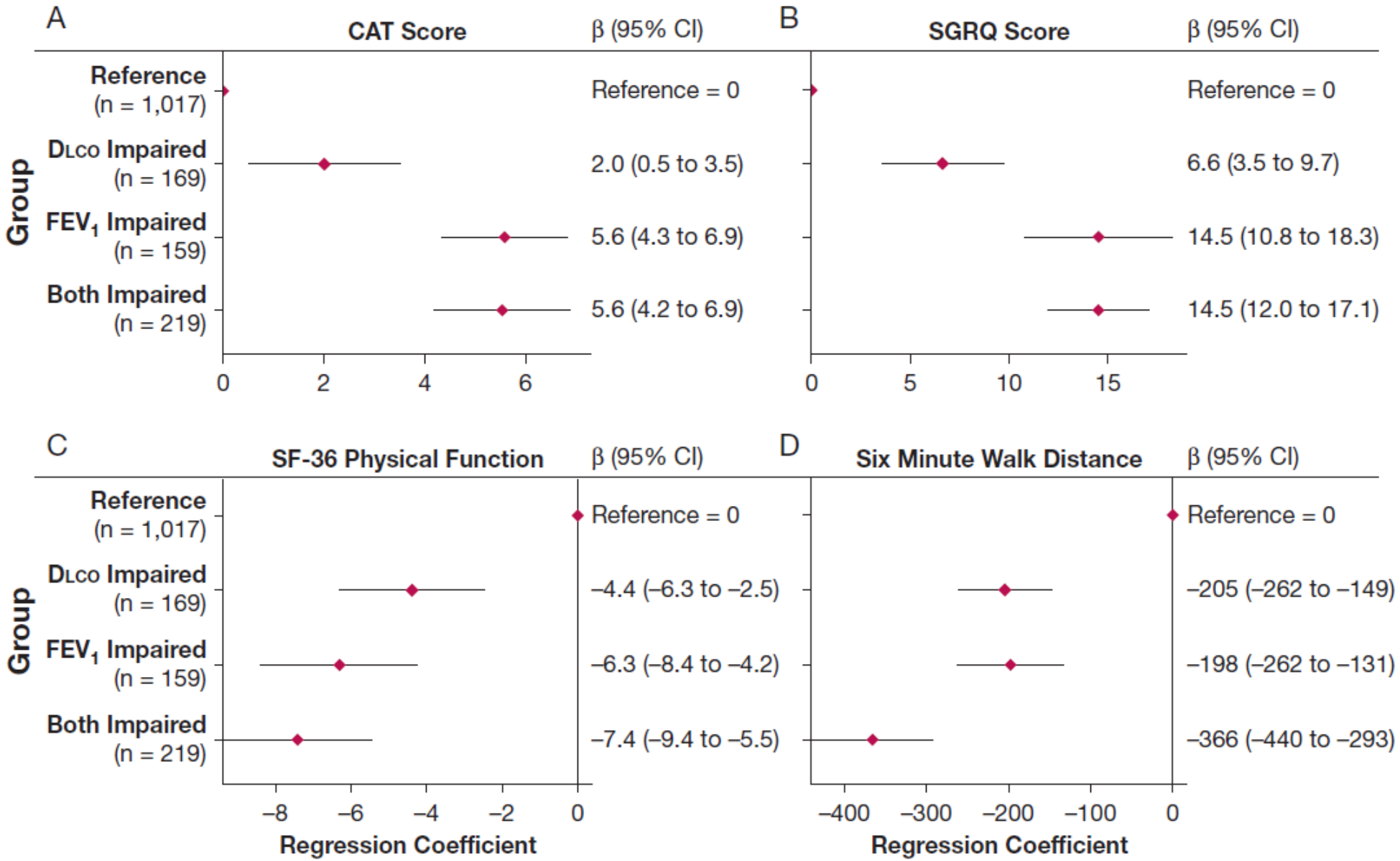
  (4) both ≤ 50% predicted.
- Outcomes was to determine whether lower DLCO is associated with increased COPD morbidity independent of emphysema assessed via spirometry and CT imaging.

Aparna Balasubramanian et al. Chest 2019; 156(6): 1111-1119.

REDUCTIONS IN DLCO AND FEV1 AND COPD MORBIDITY

	D_{LCO} % Predicted		FEV_1 % Predicted	
Outcome	Regression Coefficient (95% CI)	*P* Value	Regression Coefficient (95% CI)	*P* Value
CAT score	0.53 (0.33 to 0.73)	< .001	1.16 (0.96 to 1.36)	< .001
SGRQ score	1.67 (1.23 to 2.1)	< .001	2.94 (2.58 to 3.31)	< .001
Activity	2.58 (1.74 to 3.41)	< .001	3.99 (3.48 to 4.51)	< .001
Impact	1.3 (0.86 to 1.74)	< .001	2.25 (1.86 to 2.64)	< .001
Symptom	1.23 (0.70 to 1.76)	< .001	3.33 (2.93 to 3.72)	< .001
SF-36 Physical Function	−0.89 (−1.18 to −0.6)	< .001	−1.29 (−1.58 to −1.00)	< .001
SF-36 Mental	0.03 (−0.37 to 0.42)	.900	−0.01 (−0.31 to 0.31)	.954
6MWD, feet	−45.35 (−58.21 to −32.48)	< .001	−43.26 (−48.36 to −38.15)	< .001
Resting Spo_2, %	−0.22 (−0.38 to −0.05)	.012	−0.19 (−0.24 to −0.14)	< .001

Aparna Balasubramanian et al. Chest 2019; 156(6): 1111-1119.



Aparna Balasubramanian et al. Chest 2019; 156(6): 1111-1119.

LOW DLCO IN PATIENTS WITH GOLD STAGE 1

- Retrospective analysis from three different prospectively recruited cohorts of COPD patients followed up for a mean period of 9 years, at pulmonary clinics of tertiary university hospitals in Spain and Canada from 1995 to 2011.
- GOLD stage I COPD patients (n = 360) were enrolled and followed over 109 ± 50 months.
- Primary outcome is whether DLCO threshold can help define an increased risk of death and a different clinical presentation in these patients.
- A cutoff value for DLCO was identified for all-cause mortality and the clinical and physiological characteristics of patients above and below the threshold compared.

Juan P. de-Torres et al. Chest 2021; 160(3): 872-878.

TABLE 2] Baseline Clinical and Physiological Characteristics of COPD Patients Classified According to DLCO % of Predicted Category

Variable	DLCO ≥ 60% (n = 313) 87%	DLCO < 60% (n = 47) 13%	*P*
Age, y	62 ± 8	65 ± 9	.07
Female, %	28	46	.01[a]
Follow-up, mo	111 ± 50	95 ± 47	.04[a]
BMI	27 ± 4	25 ± 5	.01[a]
Pack-years	43 ± 25	54 ± 28	.02[a]
Active smoking, %	42	44	.85
FEV_1, % predicted	92 ± 10	90 ± 10	.38
FVC%, predicted	113 ± 14	115 ± 19	.63
FEV_1/FVC	63 ± 6	61 ± 8	.26
IC/TLC	0.40 ± 0.08	0.37 ± 0.08	.02[a]
DLCO, % predicted	86 ± 16	47 ± 10	.001[a]
Charlson score	1.2 ± 1.5	0.9 ± 1.1	.46
MRC	0.7 ± 0.7	1.1 ± 0.9	.03[a]
6MWD, m	485 ± 113	443 ± 101	.03[a]
BODE index	0.2 ± 0.6	0.5 ± 0.5	.04[a]
Exacerbations per year	0.5 ± 1.2	0.3 ± 0.7	.20
Exacerbation in previous year, %	28	20	.47
Mortality, %	9	23	.01[a]

Juan P. de-Torres et al. Chest 2021; 160(3): 872-878.

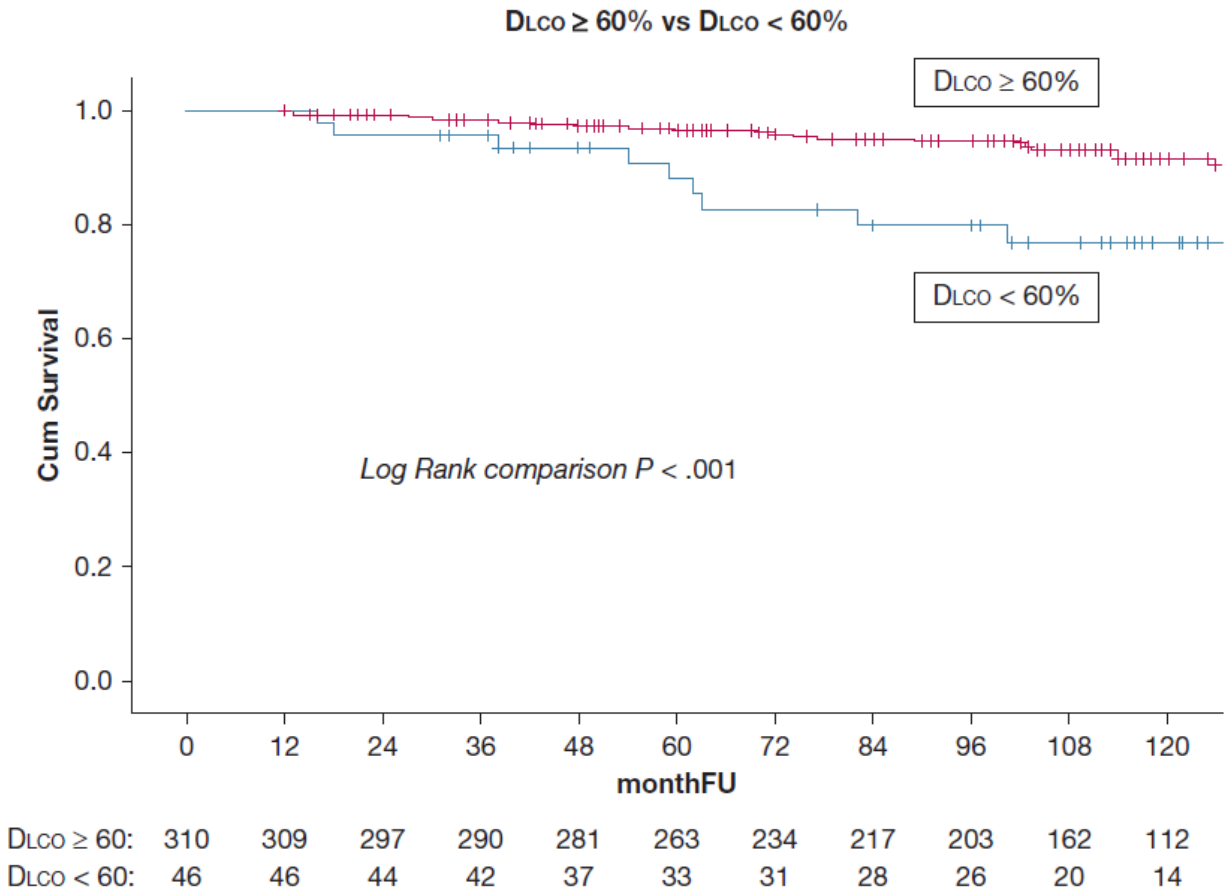


TABLE 3] Cox Proportional Analysis of the Baseline Variables Associated With All-Cause Mortality

Variable	Hazard Ratio (95% CI)	*P*
Age	1.05 (1.00-1.10)	.04
Sex	1.16 (0.41-3.32)	.77
BMI	0.97 (0.88-1.07)	.55
Pack-years	1.00 (0.99-1.01)	.23
Smoking status	1.55 (0.99-3.60)	.36
DLCO < 60%	3.37 (1.35-8.39)	.009

DLCO = diffusion capacity for carbon monoxide.

Juan P. de-Torres et al. Chest 2021; 160(3): 872-878.

TRANSFER COEFFICIENTS IN OBSTRUCTIVE LUNG DISEASES

- **KCO or DLCO/VA** is considered an index to assess the efficiency of alveolar transfer of carbon monoxide by measuring the pulmonary gas exchange across the alveolar–capillary membrane during breath-holding at full inflation in a single-breath measurement.

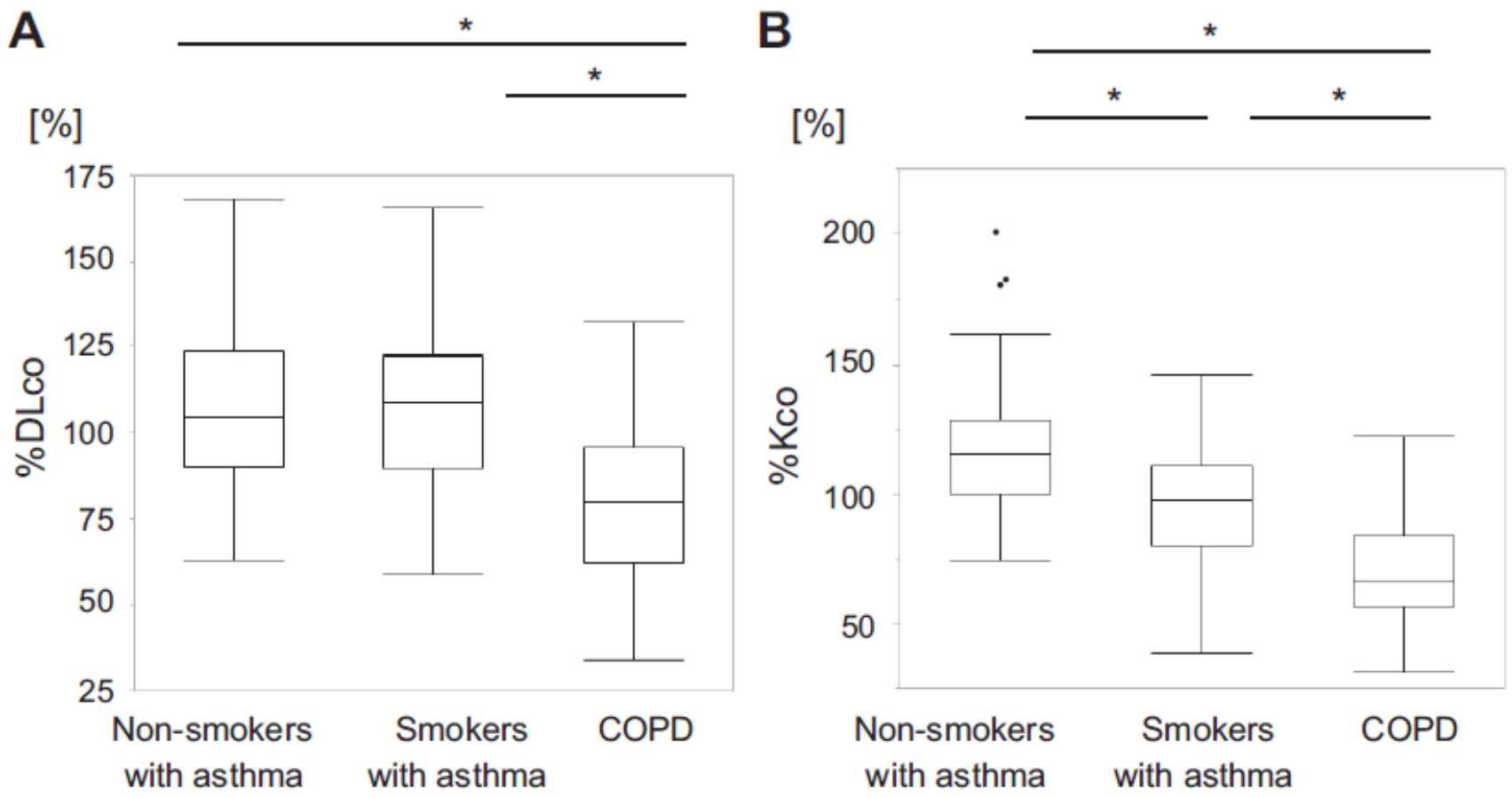
S.Kakavas et al. npj Primary Care Respiratory Medicine 2021; 31: 23.

DLCO AND KCO IN OBSTRUCTIVE LUNG DISEASES

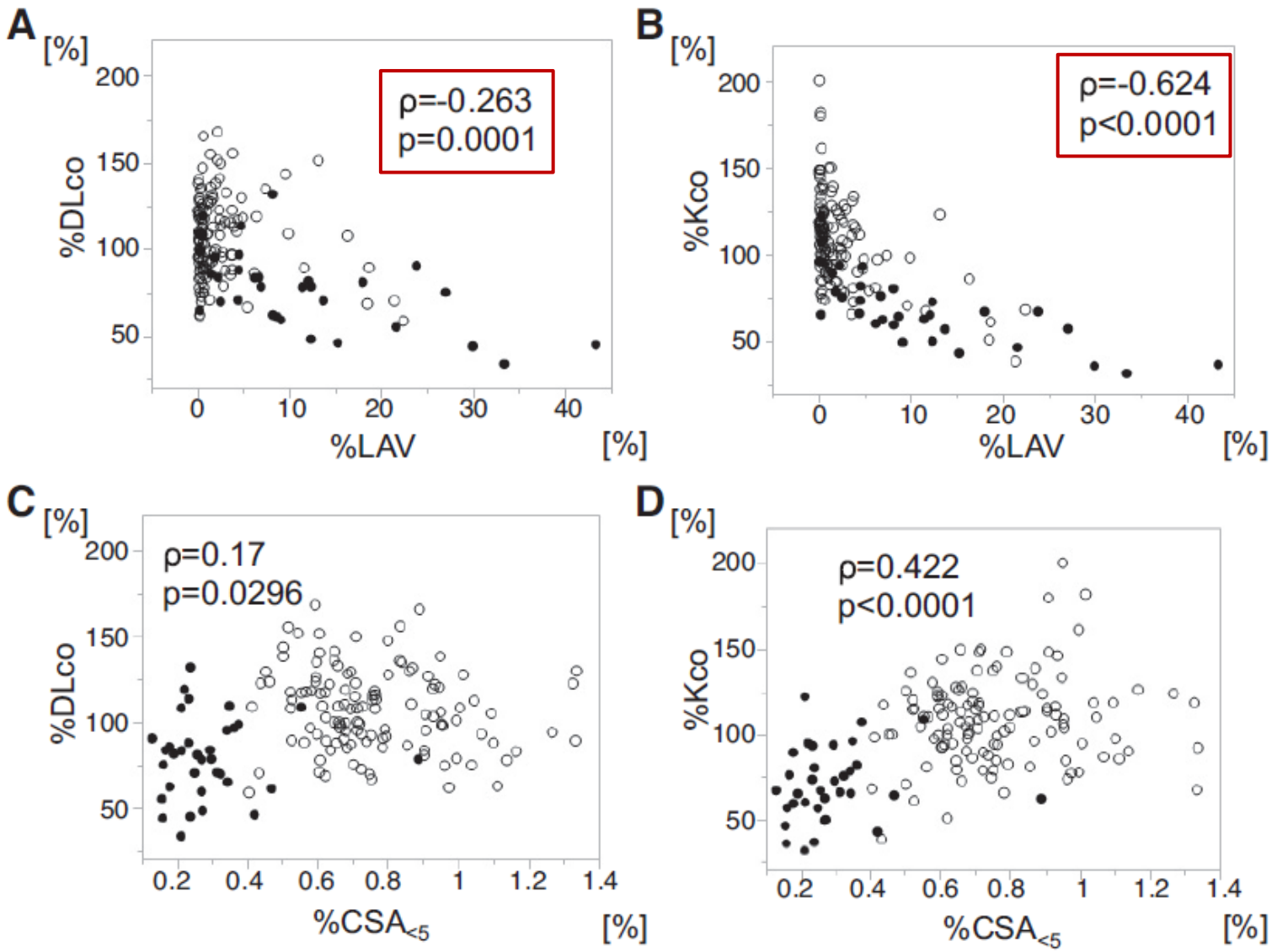
Table 2. *Characteristics of nonsmokers or smokers with asthma with prebronchodilator FEV_1/FVC of <0.7 and COPD*

	As-NS	As-Sm	COPD	*P* Value
Patients (*n*)	69	53	34	
Men/women (*n*)	16/53	43/10	29/5	<0.001
Age, yr	65.4 ± 10.6	64.9 ± 9.1	69.7 ± 8.0	NS
Pack years	1.1 ± 2.2	34.6 ± 21.7	62.0 ± 26.1	<0.001
%FVC, %	108.7 ± 17.2	109.6 ± 17.2	109.9 ± 19.3	NS
$\%FEV_1$, %	78.5 ± 16.1	75.9 ± 17.9	78.0 ± 17.9	NS
FEV_1/FVC, %	58.0 ± 7.2	56.6 ± 10.4	57.0 ± 7.3	NS
%RV, %	110.9 ± 21.5	119.3 ± 23.3	112.3 ± 26.3	NS
RV/TLC, %	38.5 ± 6.2	38.0 ± 6.6	37.7 ± 7.6	NS
%TLC, %	112.2 ± 13.7	112.2 ± 14.2	112.2 ± 14.2	NS
V_A, (men/women), liters	4.2 ± 0.6/3.1 ± 0.5	4.5 ± 0.7/3.2 ± 0.5	4.3 ± 0.8/3.7 ± 0.6	NS

Kaoruko Shimizu et al. J Appl Physiol 2018; 125: 183-189.



Kaoruko Shimizu et al. J Appl Physiol 2018; 125: 183-189.



Kaoruko Shimizu et al. J Appl Physiol 2018; 125: 183-189.

SERIAL CHANGE IN KCO IN COPD

- Data collected on the Korean Obstructive Lung Disease (KOLD) cohort were used in this study.
- We prospectively recruited patients diagnosed with obstructive lung disease from pulmonary clinics of 14 referral hospitals in Korea between June 2005 and October 2012 and followed them up for up to ten years.
- To include only COPD patients and evaluate the change in Kco, patients who met the following inclusion criteria were enrolled in the present study:

  (1) were older than 40 years

  (2) had post-bronchodilator FEV1/forced vital capacity (FVC) <0.7

  (3) were current or ex-smokers with a smoking history of over 10 pack-years

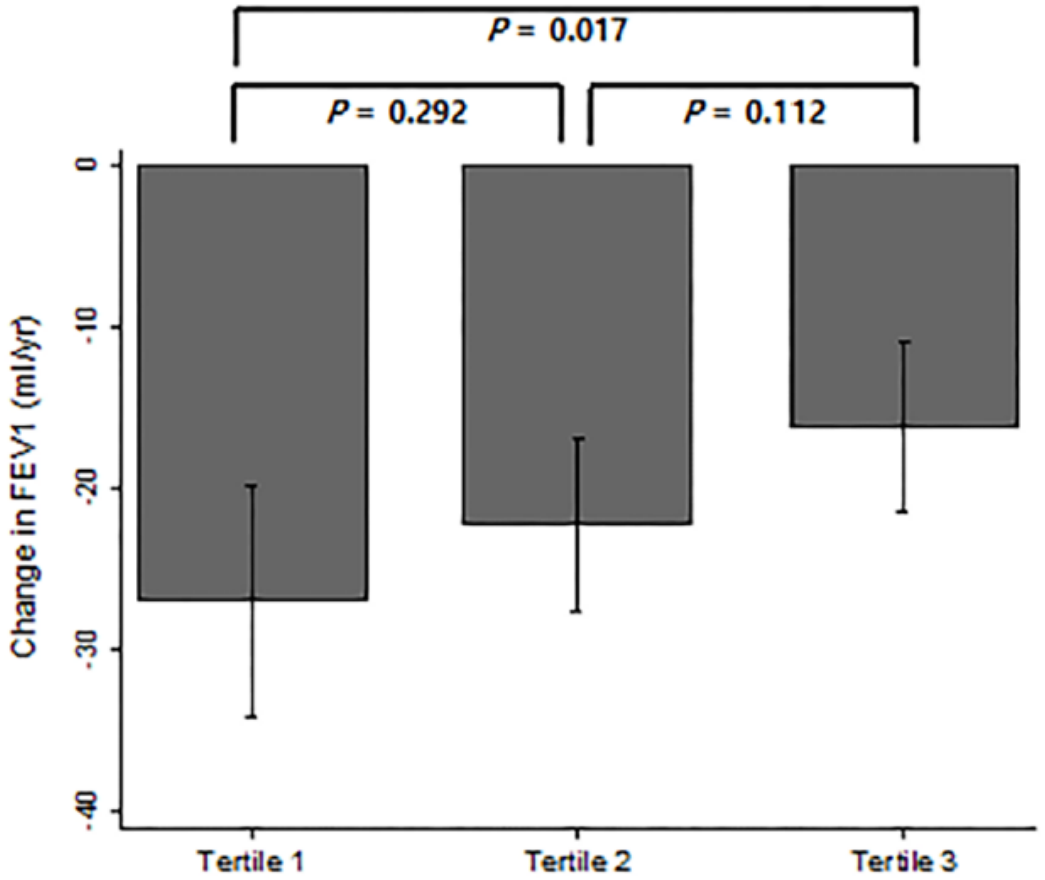
  (4) had more than two annual measures of Kco

YW Kim et al. J Clin. Med. 2020, 9, 1512.

Table 1. Baseline characteristics of patients with COPD classified by annual rates of decline in Kco.

Characteristics	Tertile 1 (Group with the Most Rapid Decline, n = 71)	Tertile 2 (n = 70)	Tertile 3 (Group with the Slowest Decline, n = 70)	p-Value *
Annual change in Kco (mmol/min/mmHg/L per year)	−0.07 ± 0.02	−0.04 ± 0.00	−0.01 ± 0.02	<0.001
Age	66.8 ± 6.8	68.1± 6.6	64.7 ± 7.4	0.014
Men, n (%)	70 (98.6)	68 (97.1)	65 (92.9)	0.180
BMI, kg/m^2	22.8 ± 2.9	22.2 ± 3.2	23.5 ± 3.3	0.079
Smoking status at baseline, n (%)				0.165
Current smokers	25 (35.2)	17 (24.3)	28 (40.0)	0.129
Former smokers	46 (64.8)	53 (75.7)	42 (60.0)	
Pack-years of smoking	51.4 ± 30.7	48.2 ± 28.6	48.6± 26.9	0.775
Total SGRQ score	37.7 ± 17.3	34.5 ± 17.0	34.1 ± 17.6	0.411
mMRC grade	1.9 ± 1.0	1.6 ± 1.1	1.6 ± 0.8	0.154
Exacerbation in previous year baseline, n (%)	13 (18.3)	19 (27.1)	13 (18.6)	0.348
Eosinophil count, cells/μL	312.8 ± 380.4	275.1 ± 192.4	313.6 ± 507.2	0.798
Hemoglobin, g/dL	14.9 ± 1.7	14.9 ± 1.1	14.9 ± 1.0	0.917
Baseline pulmonary function				
FEV1, L	1.5 ± 0.5	1.6 ± 0.5	1.6 ± 0.6	0.553
FEV1, % predicted	57.6 ± 18.2	57.9 ± 16.2	60.5 ± 19.5	0.588
FVC, L	3.5 ± 0.6	3.4 ± 0.8	3.3 ± 0.8	0.341
FEV1/FVC, %	43.8 ± 9.7	46.4 ± 10.5	49.2 ± 10.4	0.008
Bronchodilator reversibility, n (%)	9 (12.7)	7 (10.0)	10 (14.3)	0.738
Kco, mmol/min/mmHg/L	2.8 ± 0.9	2.9 ± 0.9	3.0 ± 1.0	0.539
RV/TLC, %	46.2 ± 13.1	46.0 ± 13.0	49.7 ± 13.8	0.188
Baseline CT indices				
CT emphysema index	27.7 ± 14.8	22.4 ± 16.1	18.1 ± 14.5	0.001
CT air-trapping index	94.6 ± 2.8	95.1 ± 3.6	94.2 ± 3.6	0.335
Percentage wall area, %	66.3 ± 4.8	67.7 ± 4.3	66.9 ± 5.0	0.207

YW Kim et al. J Clin. Med. 2020, 9, 1512.



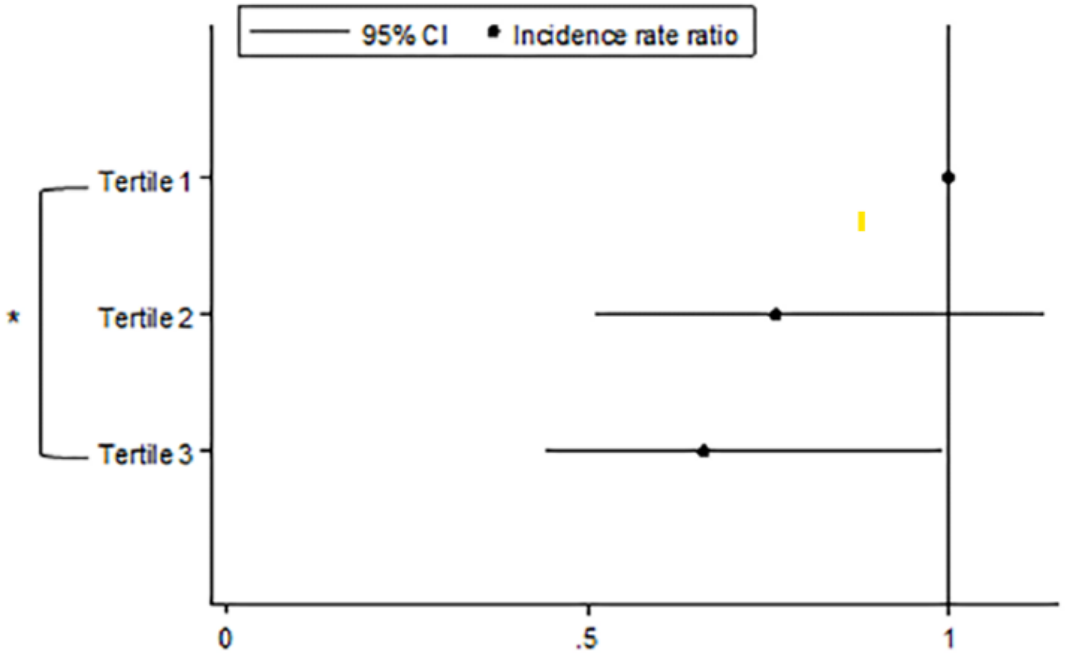


Figure. Comparison of the incidence rate of acute exacerbation according to annual rate of decline in Kco.

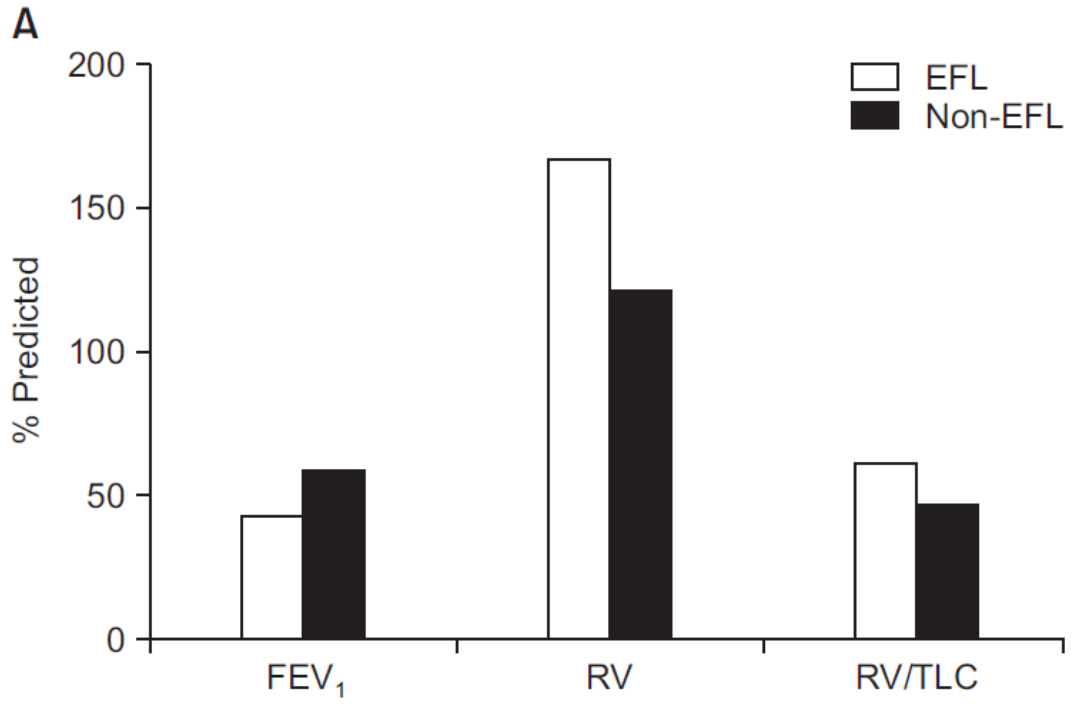
YW Kim et al. J Clin. Med. 2020, 9, 1512.

SMALL AIRWAY DYSFUNCTION IN COPD

- Small airways disease is a key feature of COPD and a major cause of airway obstruction.
- SAD is present in the early stages of COPD and becomes more widespread over time as the disease progresses to more severe COPD.
- Patients with COPD and small airways disease have worse spirometry results, more severe lung hyperinflation, and poorer health status compared with those without small airways disease, making the small airways an important treatment target.

Dave Singh. Tuberc Respir Dis 2017; 80: 317-324.
Omar S. Usmoni et al. Mayo Clin Proc. 2021; 96(9): 2448-2463.

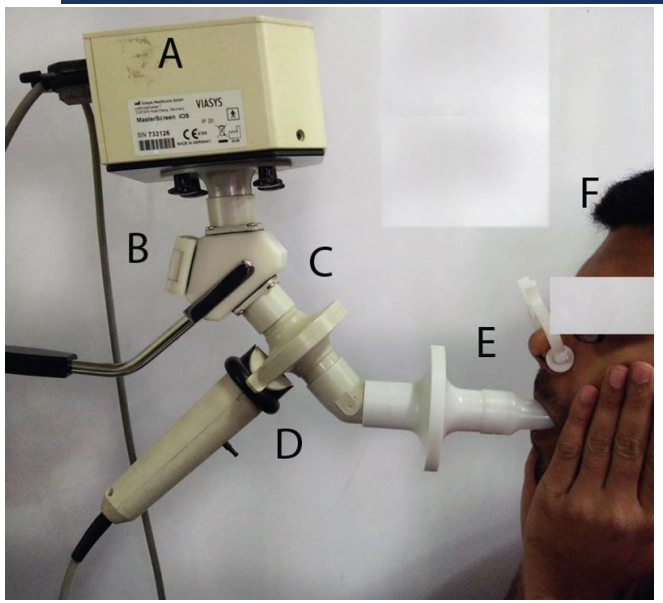
LUNG FUNCTION MEASUREMENTS IN COPD



Dave Singh. Tuberc Respir Dis 2017; 80: 317-324..

IMPULSE OSCILLOMETRY (IOS)

- IOS is a noninvasive method, which uses sound waves to measure respiratory mechanics.
- Performing the test is relatively easy since it is a passive method that requires minimal cooperation
- It measures resistance and reactance at different frequencies in lung offering important information about regional inhomogeneity and lung periphery
- Used to quantify the degree of airflow obstruction and also to distinguish between large and small airways resistance.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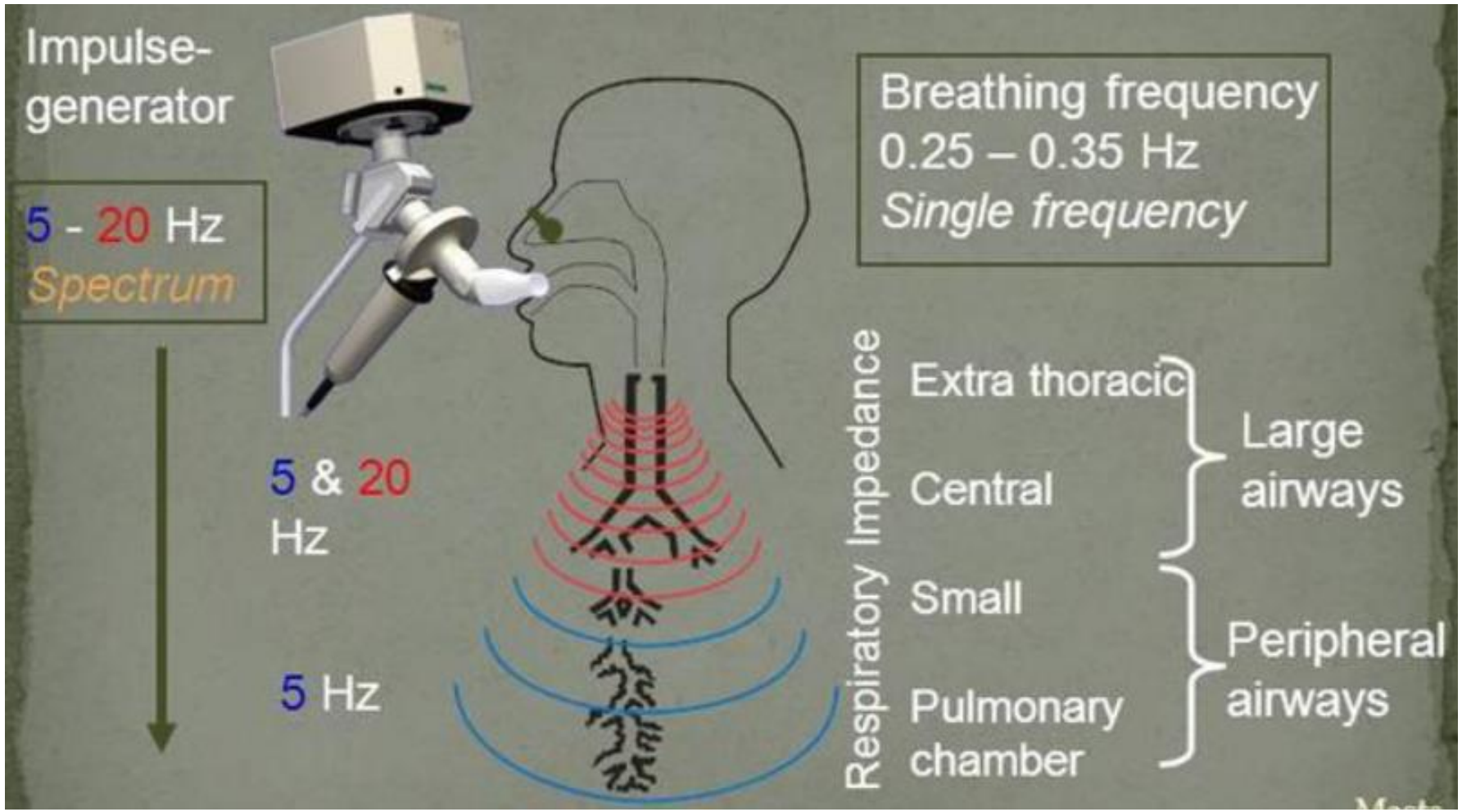

Impulse-generator
5 - 20 Hz
Spectrum
5 & 20 Hz
5 Hz
Breathing frequency
0.25 – 0.35 Hz
Single frequency
Respiratory Impedance
Extra thoracic
Central
Large airways
Small
Pulmonary chamber
Peripheral airways

IMPULSE OSCILLOMETRY IN HEALTHY AND COPD SUBJECTS

- ECLIPSE is a 3-year longitudinal prospective study designed to identify novel endpoints and compare these with FEV1 for their ability to measure and predict COPD severity and its progression over time.
- We recruited 2164 COPD subjects aged 40-75 years inclusive with a ≥10 pack-year smoking history, a post-bronchodilator FEV1 < 80% predicted and the FEV1 to FVC ratio≤ 0.70.
- We evaluated the ability of IOS to detect and stage COPD severity in the ECLIPSE cohort and contrasted with smoking and non-smoking healthy subjects.
- Additionally, we assessed whether IOS relates to extent of CT-defined emphysema.

C. Crim et al. Respiratory Medicine (2011) 105, 1069-1078.

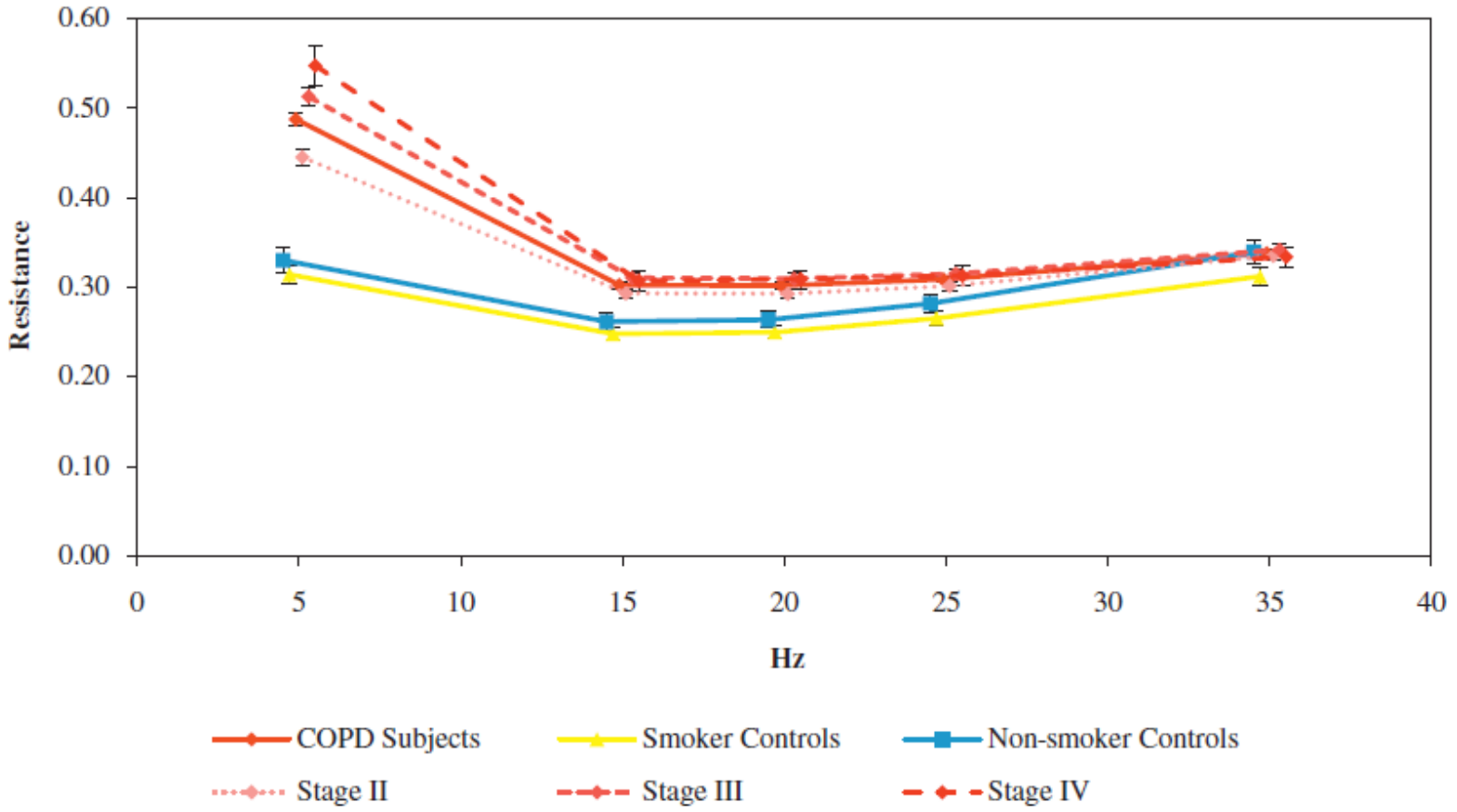
Table 1 Baseline demographics of ECLIPSE subjects.

	NSC (n = 233)	CS (n = 322)	COPD (n = 2054)	GOLD 2 (n = 915)	GOLD 3 (n = 861)	GOLD 4 (n = 278)
Age, years	54.3 (9.0)	55.2 (9.0)	63.4(7.1)[a]	63.5 (7.2)	63.7 (7.0)	62.4 (7.0)[b,c]
Male gender No. (%)	85 (36)	178 (55)[d]	1341 (65)[a]	550 (60)	584 (68)[b]	207 (74)[b,c]
BMI (kg/m^2)	27.6 (5.4)	26.8 (4.5)	26.5 (5.6)[d]	27.3 (5.7)	26.1 (5.4)[b]	25.0 (5.7)[b,c]
Current smokers No. (%)	0[e]	194 (60)[d]	746 (36)[a]	350 (38)	321 (37)	75 (27)[f]
Pack-years	0.0 (0.1)	31.5 (21.5)[d]	48.7 (27.2)[a]	48.2 (28.4)	48.9 (25.7)	50.0 (27.6)
Lung function: FEV_1 (L)	3.26 (0.78)	3.35 (0.76)	1.35 (0.52)[a]	1.75 (0.45)	1.13 (0.27)[b]	0.72 (0.16)[f]
FEV_1 (% predicted)	114.8 (13.8)	108.9 (12.0)[d]	48.4 (15.7)[a]	63.1 (8.4)	40.3 (5.8)[b]	24.8 (3.7)[f]
FEV_1/FVC (×100)	81.0 (5.2)	79.3 (5.1)	44.6 (11.6)[a]	52.7 (8.8)	40.2 (8.8)[b]	31.7 (7.3)[f]
% reversibility	2.8 (4.5)	4.5 (5.6)	10.7 (13.6)[a]	11.1 (12.5)	11.1 (14.5)	8.2 (14.0)[f]
LAA% on CT	4.1 (4.2)	2.4 (3.1)	17.7 (12.2)[a]	12.2 (9.6)	20.1 (11.6)[b]	28.6 (12.4)[f]

Table 2 Baseline IOS (impulse oscillometry) impedance parameters in ECLIPSE subjects.

	NSC[a] (n = 233)	CS (n = 322)	COPD (n = 2054)	GOLD 2 (n = 915)	GOLD 3 (n = 861)	GOLD 4 (n = 278)
R_5 (kPa/L/s)	0.33 (0.10)	0.31 (0.10)	0.49 (0.16)[b]	0.45 (0.14)	0.51 (0.16)[c]	0.55 (0.19)[d]
R_{20} (kPa/L/s)	0.26 (0.07)	0.25 (0.07)[e]	0.30 (0.08)[b]	0.29 (0.07)	0.31 (0.08)[c]	0.31 (0.09)[f]
$R_5 - R_{20}$ (kPa/L/s)	0.07 (0.05)	0.06 (0.05)	0.19 (0.10)[b]	0.15 (0.09)	0.20 (0.10)[c]	0.24 (0.12)[d]
X_5 (kPa/L/s)	−0.10 (0.06)	−0.09 (0.05)	−0.29 (0.17)[b]	−0.21 (0.13)	−0.32 (0.16)[c]	−0.44 (0.18)[d]
AX (Hz·kPa/L/s)	0.38 (0.40)	0.34 (0.35)	1.99 (1.46)[b]	1.37 (1.08)	2.25 (1.36)[c]	3.23 (1.79)[d]
F_{Res} (Hz)	12.4 (3.4)	12.1 (3.2)	20.7 (5.2)[b]	18.3 (4.3)	21.8 (4.7)[c]	25.3 (5.5)[d]

RESISTANCE AS A FUNCTION OF FREQUENCY FOR CONTROL AND ALL COPD SUBJECTS



C. Crim et al. Respiratory Medicine (2011) 105, 1069-1078.

IOS AS AN ALTERNATIVE DIAGNOSTIC METHOD FOR COPD

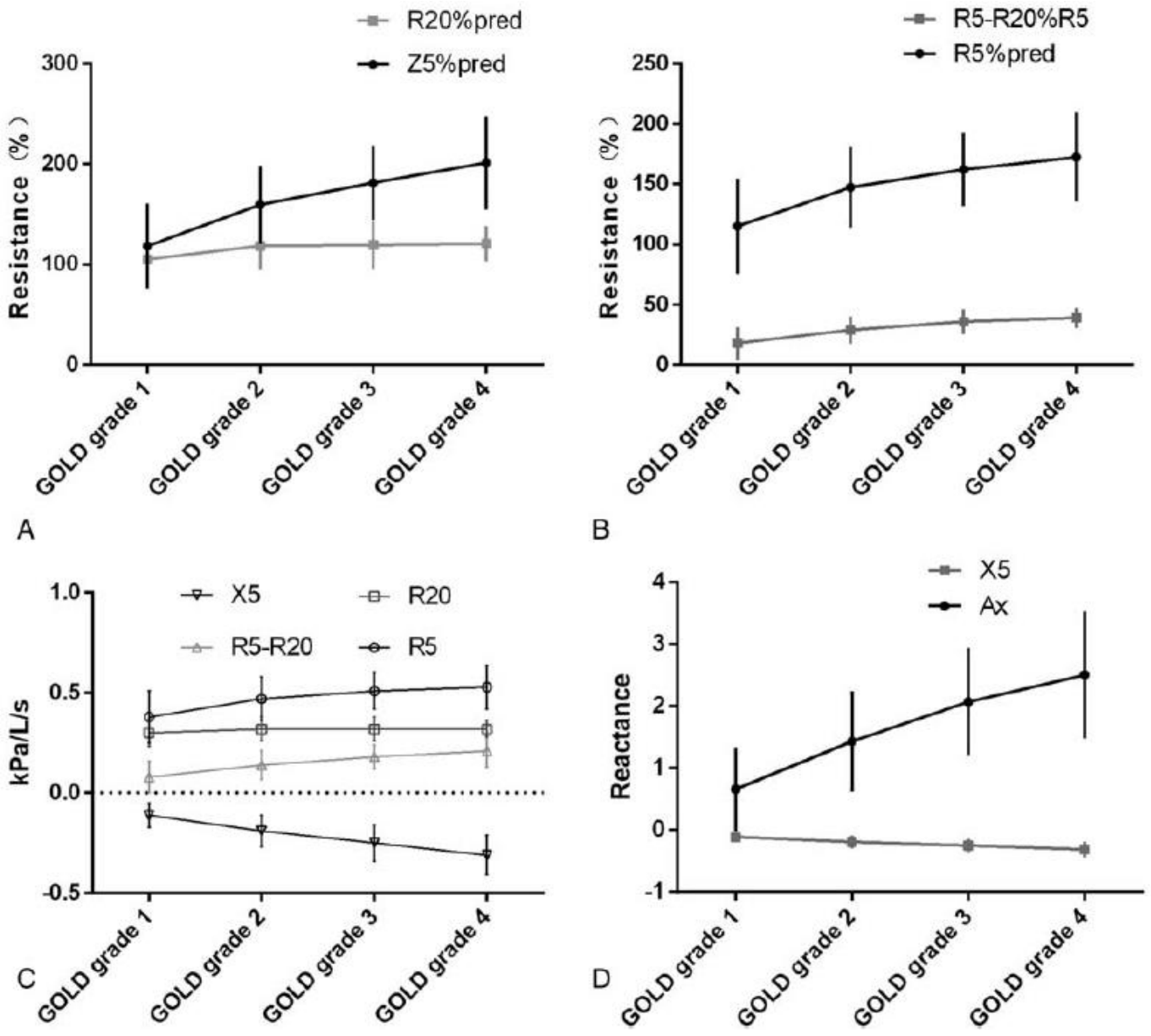
- Patients with COPD who were admitted to the Ninth Hospital of Xi'an Affiliated Hospital of Xi'an Jiaotong University between October 2014 and September 2016, and who met the GOLD diagnostic criteria (FEV1/FVC<70% after bronchodilator inhalation) were included in this study.
- Depending on the severity of airflow obstruction, that is, based on FEV1%Pred, patients were divided into groups: GOLD grade 1 FEV1%pred≥80%; grade 2 50%FEV1%pred <80%; grade 3 30%FEV1%pred <50%; and grade 4 FEV1%pred<30%.

Medicine 2017; 96: 46 (e8543).

Traditional pulmonary function tests and IOS parameters of patients with COPD disaggregated by severity grade and one-way analysis of variance.

	GOLD classification					ANOVA	
	Grade 1–4 n=215	Grade 1 n=18	Grade 2 n=83	Grade 3 n=78	Grade 4 n=36	F	P
BMI, kg/m^2	23.25±3.86	22.39±3.05	24.42±3.73*	22.23±4.07†	23.23±3.41	4.92	.003
Acute exacerbations in the past 12 mo	0.78±1.22	0.5±0.79	0.37±0.91	1±1.35†	1.36±1.42*,†	7.59	<.001
mMRC	1.7±1.11	1.11±0.96	1.34±0.97	1.94±1.06*,†	2.31±1.17*,†	10.77	<.001
N%	70.37±13.31	63.29±14.57	69.57±12.54	71.12±14.6*	74.13±10.01*	2.91	.035
FEV1/FVC, %	52.42±9.88	64.41±2.73	58.21±6.19*	48.62±7.03*,†	41.32±9.03*,†,‡	77.41	<.001
FEV1%pred	48.70±18.41	84.52±11.6	60.17±7.84*	39.44±5.92*,†	24.43±4.23*,†,‡	408.79	<.001
MMEF 75%–25%	20.89±10.47	41.22±9.22	26.67±6.71*	15.3±3.17*,†	9.5±2.55*,†,‡	198.53	<.001
MEF50%	19.9±10.83	40.23±8.98	26.17±6.99*	13.62±3.09*,†	8.86±4.87*,†,‡	184.02	<.001
KCO, mmol/min/kPa/L	80.84±26.57	83.61±19.4	86.63±24.69	79.68±26.7	68.58±29.94*,†,‡	4.16	.007
RV/TLC, %	55.68±9.96	45.73±8.38	51.24±7.59*	58.12±8.07*,†	65.99±8.63*,†,‡	39.46	<.001
Z5%pred	170.98±43.87	118.49±40.62	159.52±37.45*	181.29±35.35*,†	201.31±44.97*,†,‡	23.12	<.001
R5, kPa/L/s	0.48±0.11	0.38±0.13	0.47±0.11*	0.51±0.09*,†	0.53±0.11*,†	9.46	<.001
R5%pred	154.19±35.46	115.05±38.45	147.34±32.3*	162.13±29.05*,†	172.36±35.9*,†	15.38	<.001
R20, kPa/L/s	0.32±0.06	0.3±0.07	0.32±0.06	0.32±0.06	0.32±0.04	0.83	.481
R20%pred	118.18±21.77	105.04±24.67	118.65±22.11*	119.48±22.25*	120.85±16.31*	2.53	.059
R5-R20, kPa/L/s	0.16±0.08	0.08±0.08	0.14±0.07*	0.18±0.06*,†	0.21±0.08*,†	18.42	<.001
R5-R20/R5	0.32±0.11	0.18±0.12	0.29±0.10*	0.36±0.09*,†	0.39±0.07*,†	26.48	<.001
Fres, Hz	21.65±4.72	15.13±4.51	20.36±3.42*	23.07±4.05*,†	24.83±4.72*,†,‡	29.93	<.001
Ax, kPa/L	1.77±0.98	0.66±0.65	1.43±0.79*	2.07±0.84*,†	2.5±1.0*,†,‡	27.93	<.001

Medicine 2017; 96: 46 (e8543).



Medicine 2017; 96: 46 (e8543).

Results of Spearman correlation analysis showing correlation between traditional pulmonary function parameters and IOS parameters.

	FEV1	FEV1%pred	FEV1/FVC	MEF50%pred	MMEF 75%–25%pred	KCO	RV/TLC
Z5%pred	−.322**	−.435**	−.391**	−.379**	−.439**	0.117	.268**
R5%pred	−.253**	−.350**	−.311**	−.291**	−.354**	.166*	.189**
R5	−.297**	−.292**	−.248**	−.266**	−.323**	.192**	.217**
R20%pred	0.010	−0.104	−0.100	−0.031	−0.108	.258**	−0.060
R20	−0.056	−0.038	−0.018	−0.001	−0.062	.291**	−0.015
R5-R20	−.421**	−.425**	−.362**	−.414**	−.452**	0.041	.346**
(R5-R20)%R5	−.449**	−.474**	−.408**	−.474**	−.489**	−0.090	.398**
X5	.493**	.540**	.470**	.525**	.569**	0.015	−.436**
Fres	−.470**	−.500**	−.475**	−.503**	−.510**	−0.051	.350**
Ax	−.488**	−.521**	−.460**	−.504**	−.540**	0.001	.401**

*$P < .05$; **$P < .01$. Ax = reactance area, EV1/FVC = forced expiratory volume in one second/forced vital capacity, FEV1 = forced expiratory volume in one second, Fres = frequency response, IOS = impulse oscillometry system, KCO = ratio of carbon monoxide diffusion capacity to alveolar ventilation (DLCO/VA), MEF50% = maximal expiratory flow in 50% vital capacity, MMEF75%–25% = maximal mid expiratory flow, %pred = of the predicted value, R20 = resistance at 20 Hz, R5 = resistance at 5 Hz, RV/TLC = residual volume/total lung capacity, X5 = reactance at 5 Hz, Z5 = Total respiratory impedance.

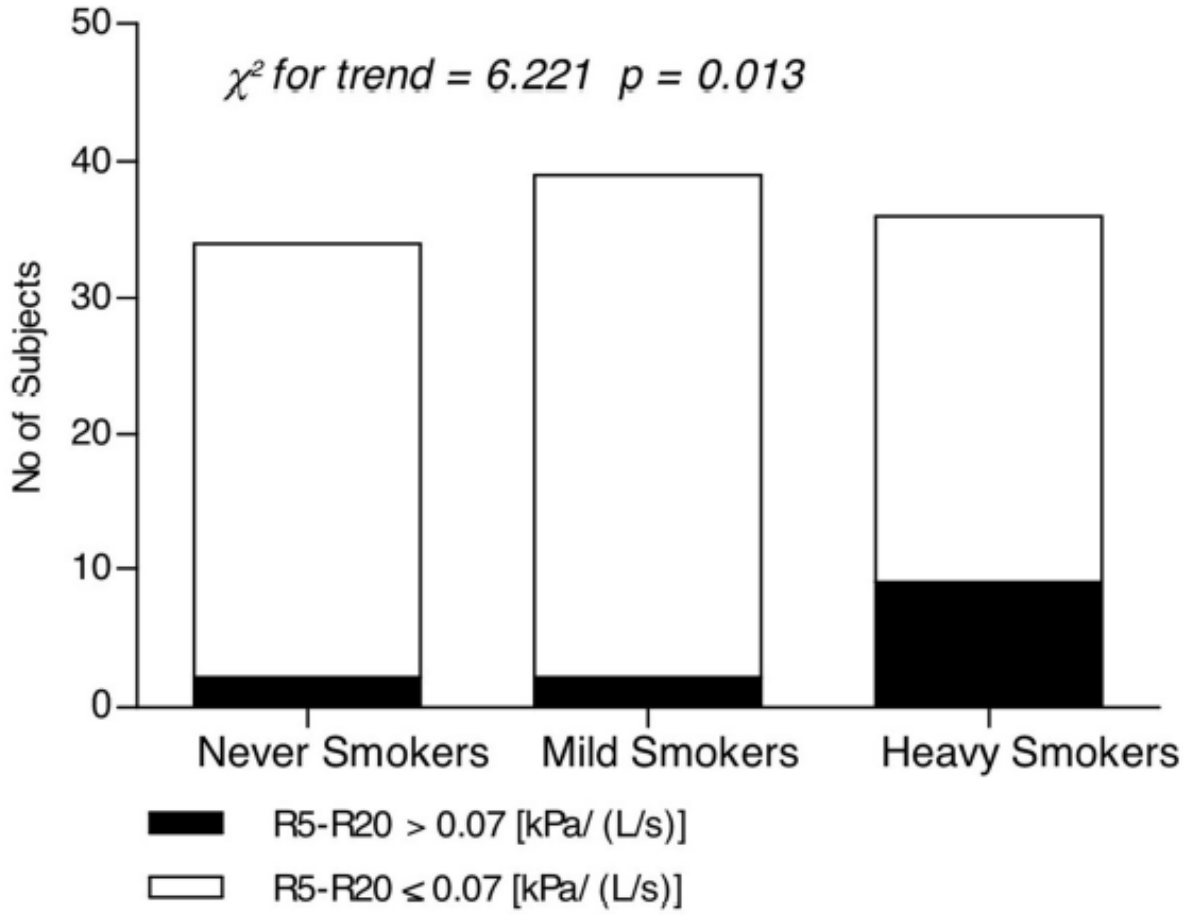
Medicine 2017; 96: 46 (e8543).

DETECTION OF SAD IN ASYMPTOMATIC SMOKERS WITH PRESERVED SPIROMETRY

- Single-center, observational cross-sectional study conducted in a single session between October 2018 and December 2019 at the Lung Function Unit of University Hospital of Parma.
- Included 75 asymptomatic smokers (37 females, mean age 47 ± 12 years, 26 ± 17 pack/year) with preserved spirometry [(FEV1)/(FVC) ≥0.70 and normal FVC] and 34 never-smokers (19 females, mean age 42 ± 15 years).
- To investigate the value of using the impulse oscillometry system (IOS) to detect SAD in asymptomatic smokers with preserved spirometry.

Roberta Pisi et al. Int J COPD 2021; 16: 2585-2590.

	Ne		36)	p
Age (yr)				<0.01*
Sex (F%)				n.s.
BMI (Kg/m^2)				<0.01*
Pack/year				…
FVC (% pred)				<0.01#
FEV1 (% pred)				<0.01*
FEV1/FVC (%)				<0.01*
FEV3/FEV6 (%)				<0.01*
FEF25-75 (% pred)				<0.01§
R5 (kPa·s·L^{-1})				<0.05*
R20 (kPa·s·L^{-1})				n.s.
R5-R20 (kPa·s·L^{-1})				<0.01*
AX (kPa·L^{-1})				n.s.
X5 (kPa·s·L^{-1})				<0.05*
FRes (Hz)				n.s.



Notes: Values are expressed as mean ± SD, median [25–75% percentile] or %. Bold text indicates statistical significance. *Heavy Smokers vs Healthy Subjects and Mild Smokers, #Heavy Smokers vs Healthy Subjects, §Heavy Smokers vs Mild Smokers.

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IOS FOR DETECTION OF SAD IN PTS WITH SYMPTOM AND PRESERVED LUNG FUNCTION

- This was a single-centered, observational study in which subjects were recruited and tested at the Pulmonary Function Laboratory of West China Hospital, Sichuan University, Chengdu, China between May 1st and September 1st, 2020.
- Included in this study, subjects had to be aged over 18 years and came to receive pulmonary function tests because of **chronic respiratory symptoms**.
- Subjects were eligible when they fulfill the criteria of PPF (**FEV1/FVC** $\geq$ **0.70**).

LY Li et al. Respir Res (2021) 22; 68.

Table 1 Characteristics of healthy controls and subjects with chronic respiratory symptoms and PPF

	Symptomatic subjects with PPF (n = 209)	Healthy controls (n = 85)	P value
Demographics			
Age (years)	39.53 ± 12.79	36.92 ± 10.21	0.067
BMI (kg/m^2)	22.09 ± 3.12	22.68 ± 2.57	0.123
Sex: male, n (%)	97 (46.4)	40 (47.1)	0.920
Spirometry			
FEV_1 (% predicted)	104.61 ± 12.41	106.58 ± 10.73	0.201
FVC (% predicted)	105.90 ± 13.09	106.65 ± 12.85	0.656
FEV_1/FVC	83.78 ± 6.97	85.16 ± 5.81	0.108
$FEF_{25-75\%}$ (% predicted)	86.48 ± 22.71	93.02 ± 21.01	0.023
$FEF_{50\%}$ (% predicted)	90.98 ± 22.95	100.53 ± 22.64	0.001
$FEF_{75\%}$ (% predicted)	81.37 ± 30.57	85.50 ± 27.61	0.281
IOS			
R5 (kPa/L s)	0.32 ± 0.07	0.28 ± 0.06	< 0.001
R20 (kPa/L s)	0.29 ± 0.06	0.26 ± 0.06	< 0.001
R5–R20 (kPa/L s)	0.0219 ± 0.0273	0.0193 ± 0.0238	0.449
X5 (kPa/L s)	− 0.1009 ± 0.0279	− 0.1007 ± 0.0280	0.966
Fres (Hz)	11.38 ± 2.58	10.49 ± 2.10	0.005
AX (kPa/L)	0.24 (0.17, 0.34)	0.20 (0.14, 0.30)	0.015

The data are presented as mean ± SD for normally distributed variables and median (interquartile range) for nonnormally distributed variables

BMI body mass index

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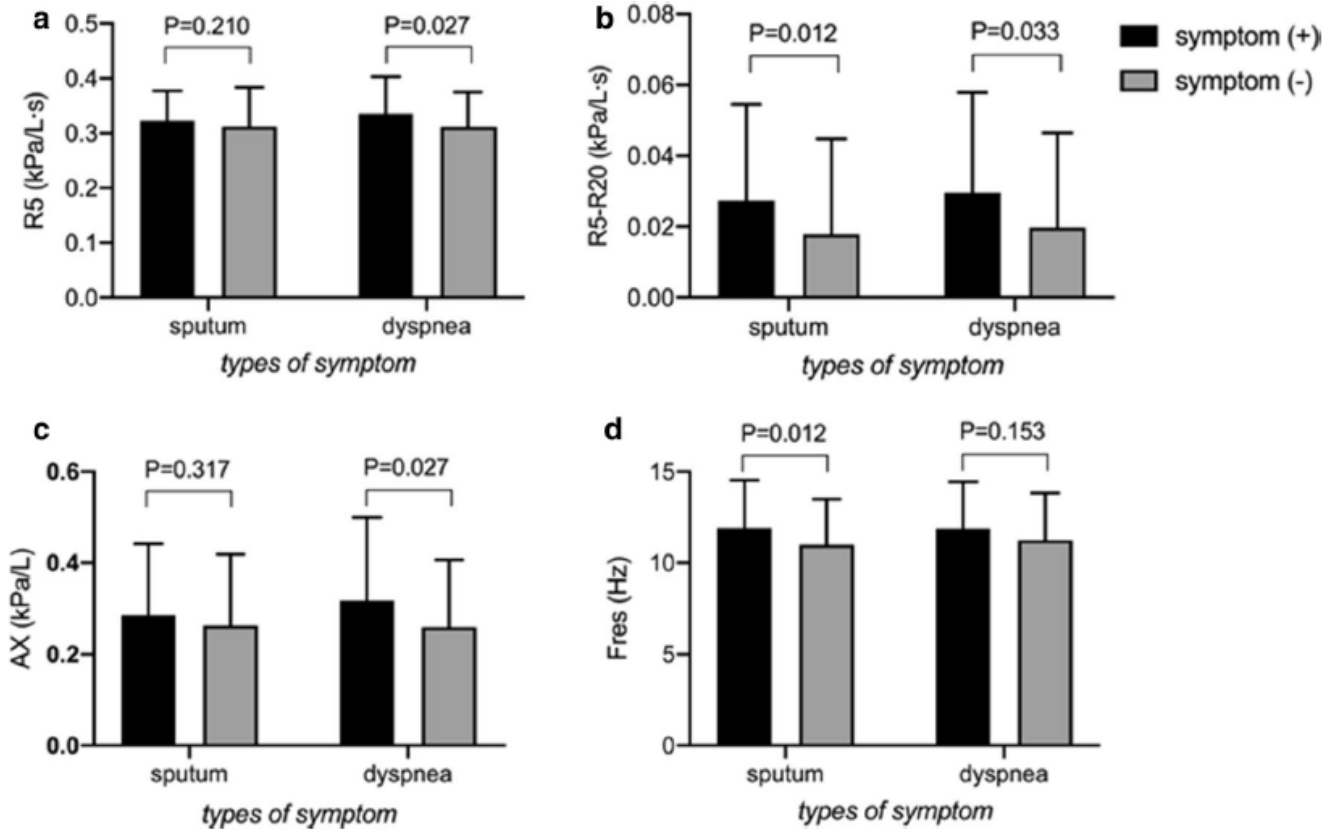

Spirometry parameter	FEV_1%	FVC %	FEV_1 /FVC	$FEF_{25-75\%}$ %	$FEF_{50\%}$ %	$FEF_{75\%}$ %
mMRC	− 0.004	0.021	− 0.072	− 0.082	− 0.084	− 0.126
CAT	0.029	0.112	− 0.188**	− 0.135	− 0.124	− 0.169*
IOS parameter	**R5**	**R20**	**R5–R20**	**X5**	**AX**	**Fres**
mMRC	0.150*	0.111	0.162*	− 0.127	0.179**	0.131
CAT	*0.243***	0.174*	0.150*	− 0.200**	*0.204***	*0.212***

SUMMARY

- Airway obstruction is the hallmark of COPD, diagnosed by simple spirometry.
- The criteria of post BD FEV1/FVC<0.70 or LLN may cause misclassification in some populations.
- COPD has various aspects of pathologic mechanisms.
- Novel non-contact early airflow limitation screening system (**EAFL-SS**)
- Air trapping, representing as RV/TLC, is closely associated with exacerbations.
- DLCo, KCO are related with COPD morbidity, patients' symptom, exercise tolerance, and exacerbations.
- IOS is an alternative diagnostic method of COPD.