“Hot Issues in Respiratory Medicine” Small airway disease as novel target of evaluation and treatment in COPD

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Small airway disease in COPD

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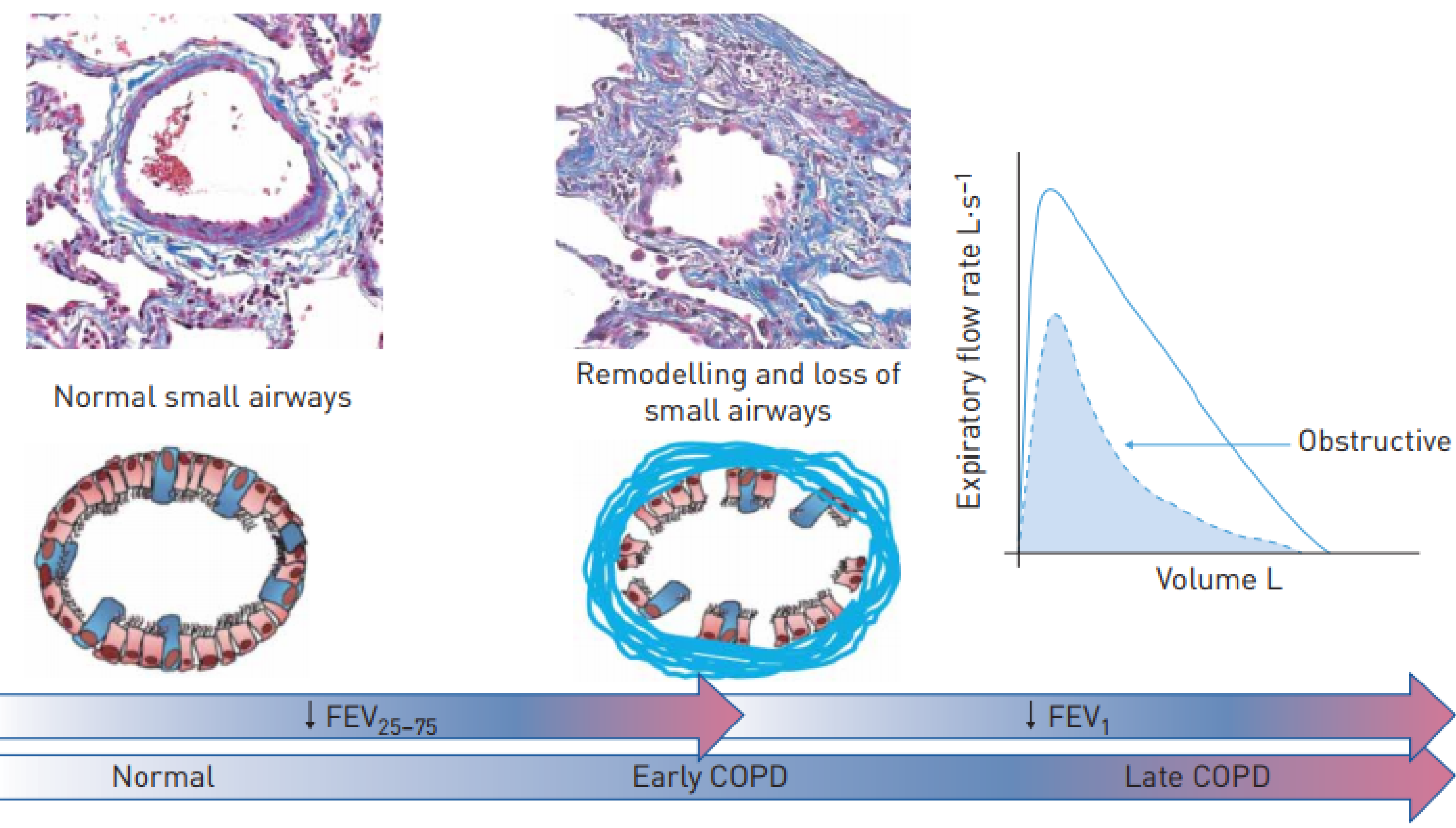
In COPD, airflow obstruction is caused by a mixture of small airways disease (which increases airway resistance) and parenchymal destruction (emphysema, that reduces the normal elastic recoil of the lung parenchyma), the relative contributions of which vary from person to person.

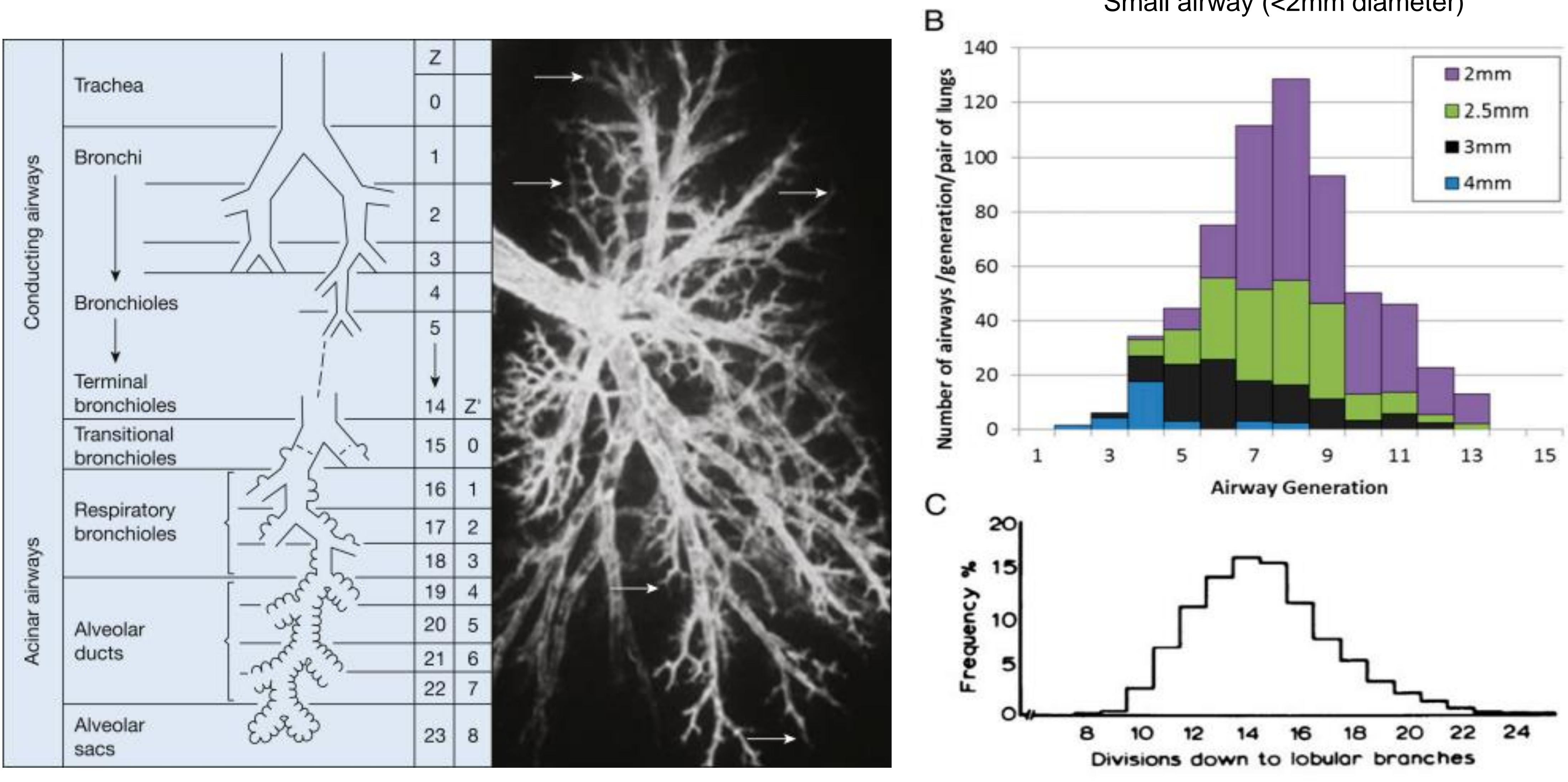
Chronic inflammation causes structural changes, narrowing of the small airways, luminal exudates in the small airways and destruction of the lung parenchyma that leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil. In turn, these changes diminish the ability of the airways to remain open during expiration. A loss of small airways may also contribute to airflow obstruction and mucociliary dysfunction.



Pathology samples of respiratory biopsies.

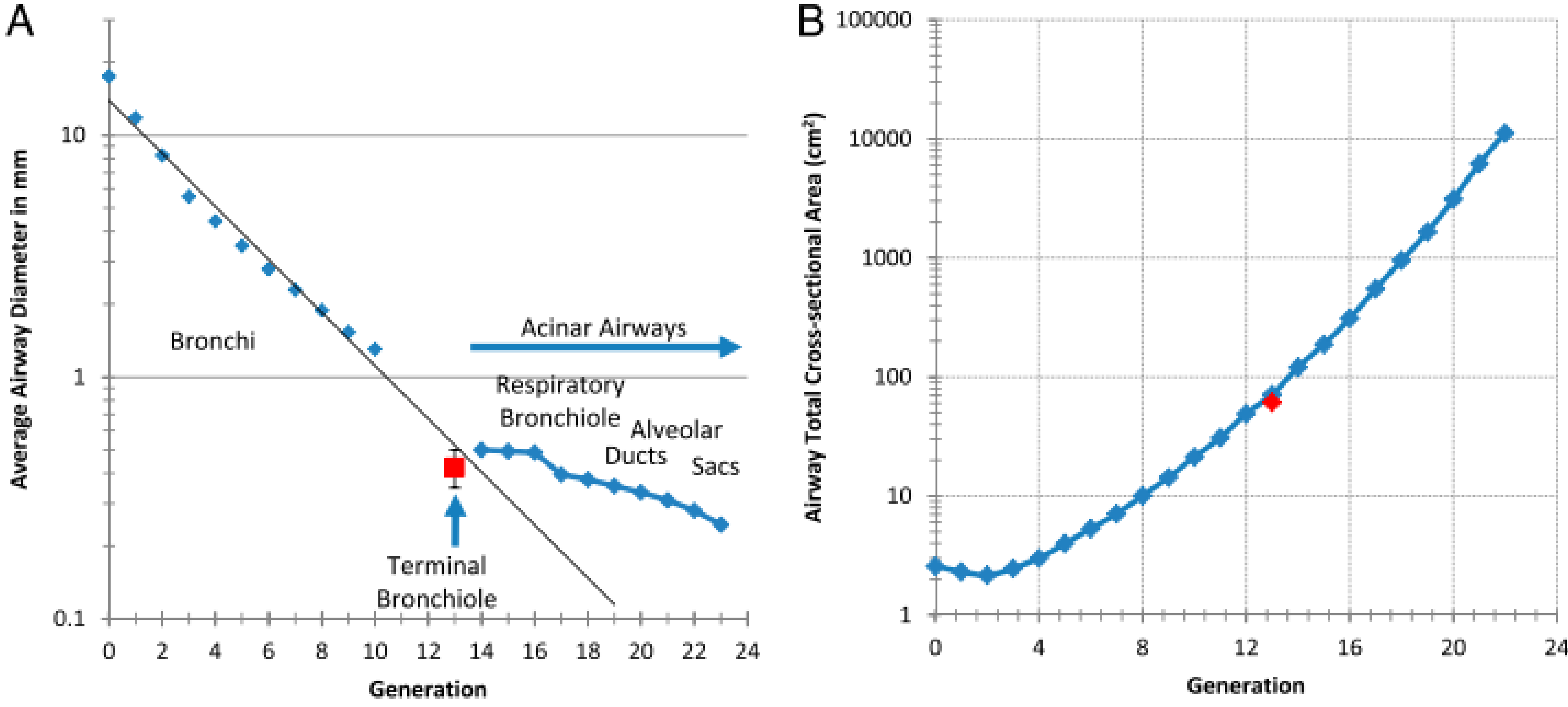
* $FEF_{25–75}$ is highly sensitive to early lung changes leading to airflow limitation

Eur Respir J. 2020 Mar 5;55(3):1902457



Bronchogram from a normal human lung

CHEST 2013; 143(5): 1436 – 1443



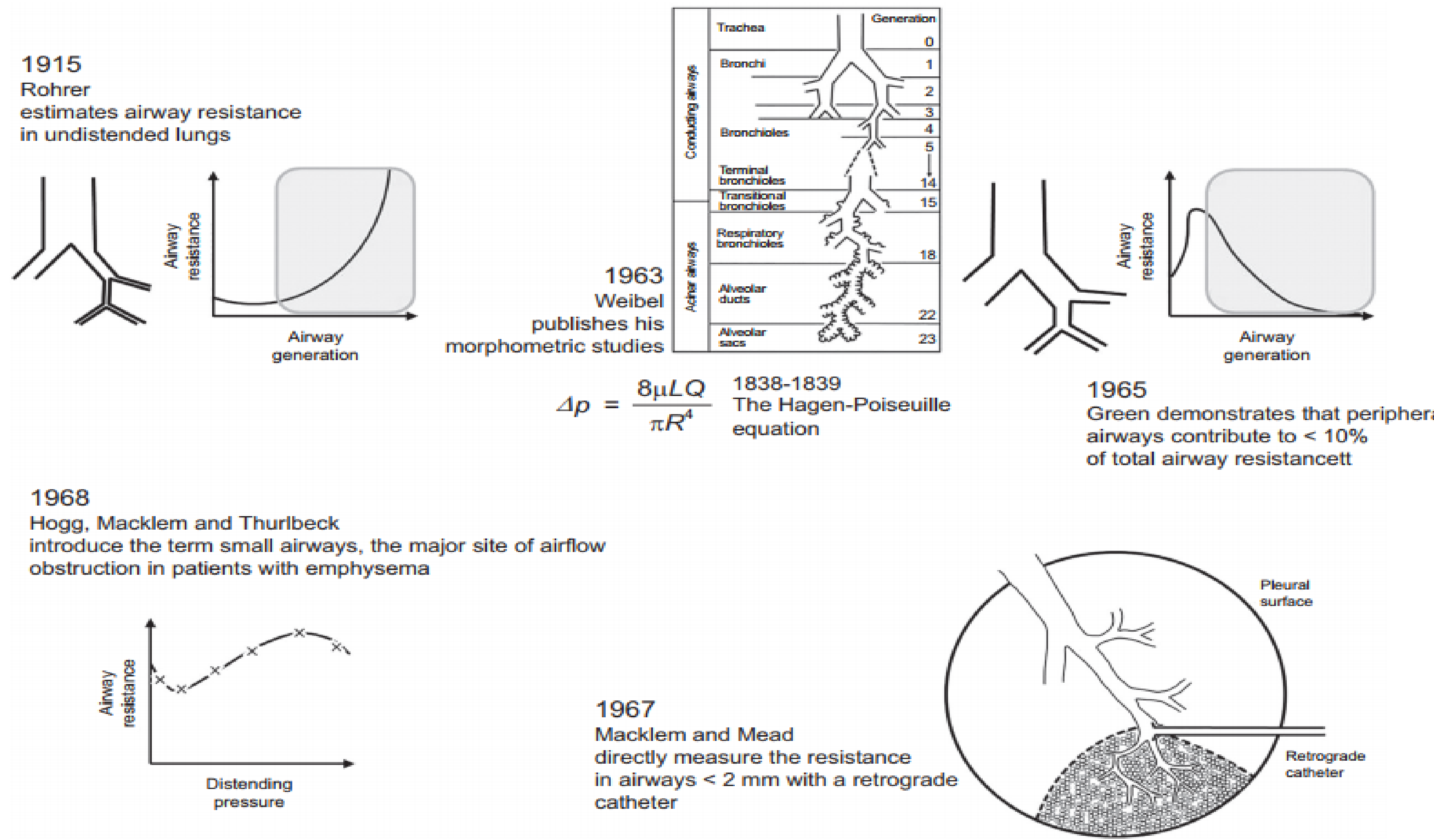
CHEST 2013; 143(5): 1436 – 1443

Evidence for small airway disease in COPD

1. Direct assessment of small airway resistance
2. Pathology studies
3. Lung physiology
4. Imaging studies

Tuberc Respir Dis 2017;80:317-324

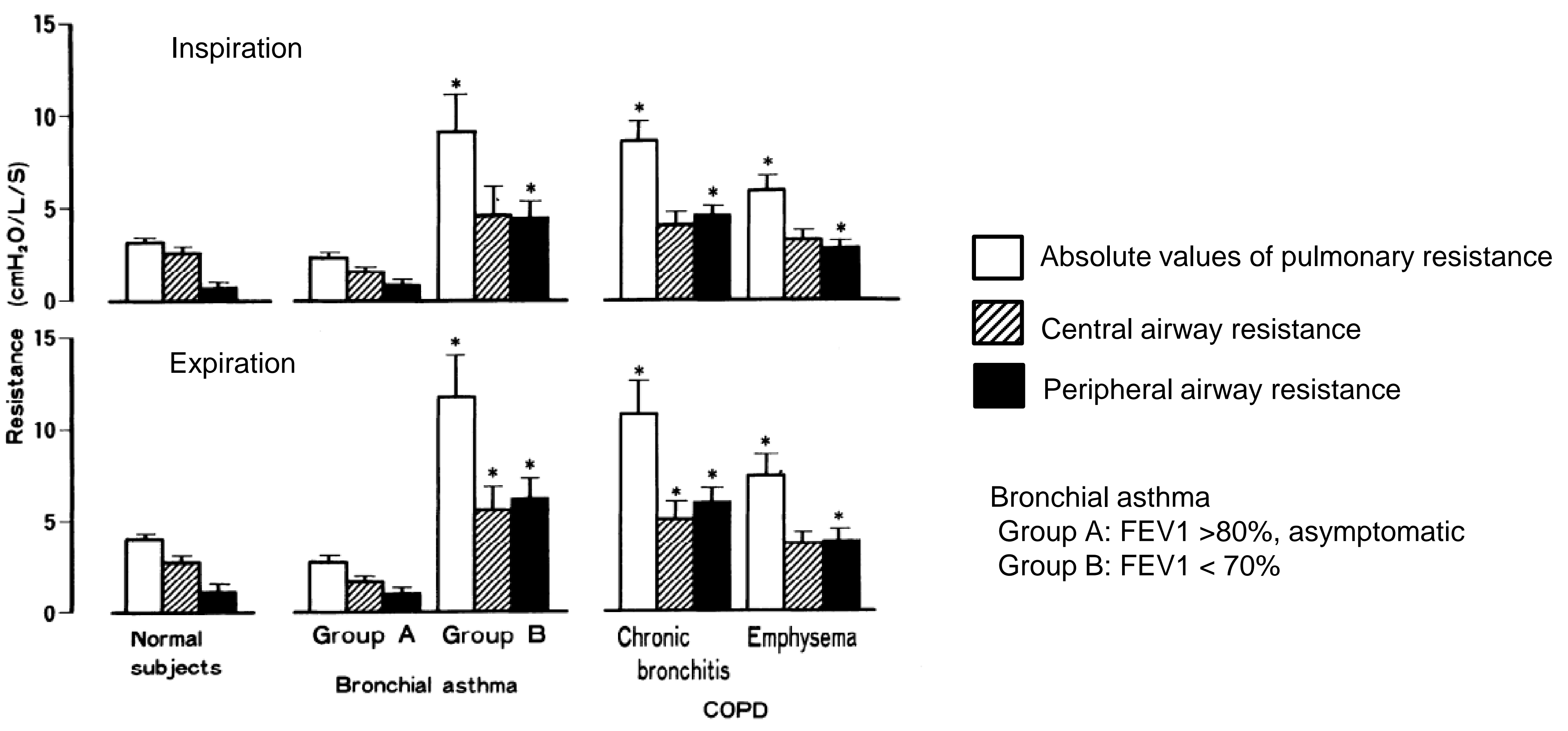
Direct assessment of small airway resistance



Brief historical overview showing the milestones that lead to the discovery of the nature of airway resistance and to small airways mechanics.

Respir Care. 2020 Sep;65(9):1392-1412

Direct assessment of small airway resistance



J Appl Physiol (1985). 1992 Mar;72(3):1016-23

Direct assessment of small airway resistance

Table 1— ***Summary of Direct Measurements of Total and Peripheral Airways Resistance in Human Lungs***

	Control		Emphysema		Chronic Bronchitis[a]	
Source	Total	Peripheral	Total	Peripheral	Total	Peripheral
Hogg et al[7]	0.69 ± 0.04	0.18 ± 0.04	3.66 ± 0.99	2.97 ± 0.93	...	...
Van Brabandt et al[23]	1.52 ± 0.27	1.24 ± 0.27	10.47 ± 3.79	9.44 ± 3.42	...	...
Yanai et al[14]						
Inspiration	3.1 ± 0.1	0.7 ± 0.3	5.9 ± 0.8	2.8 ± 0.4	8.7 ± 1.1	4.6 ± 0.5
Expiration	4.0 ± 0.3	1.1 ± 0.4	7.3 ± 1.1	3.7 ± 0.6	10.6 ± 1.8	5.9 ± 0.8
Wagner et al[24]/1990	...	0.15 ± 0.03	...	...	...	...
Wagner et al[25]/1998	...	0.18 ± 0.05	...	...	...	...

Mean ± SE. All units are cm H_2O/L/s. The original Macklem and Mead data can be found in Reference 13. References in the Source column refer to studies where direct measurements of peripheral airways resistance have been reported.

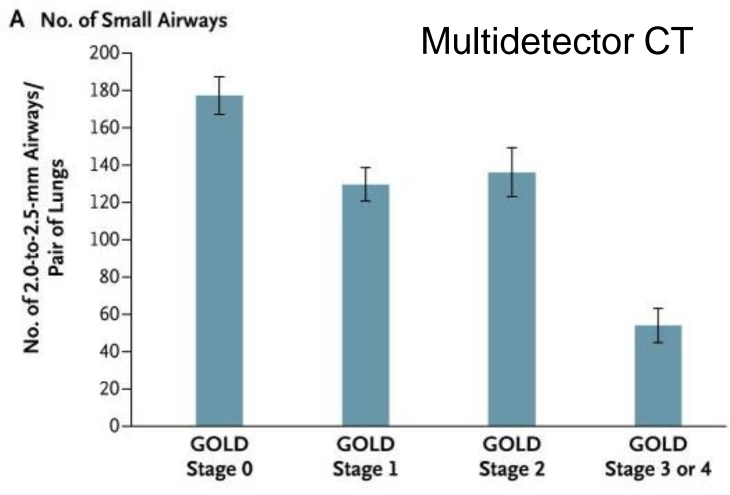
[a] Although the authors referred to these cases as chronic bronchitis, the obstruction was most likely attributable to the bronchiolitis present in some but not all cases of chronic bronchitis.[14]

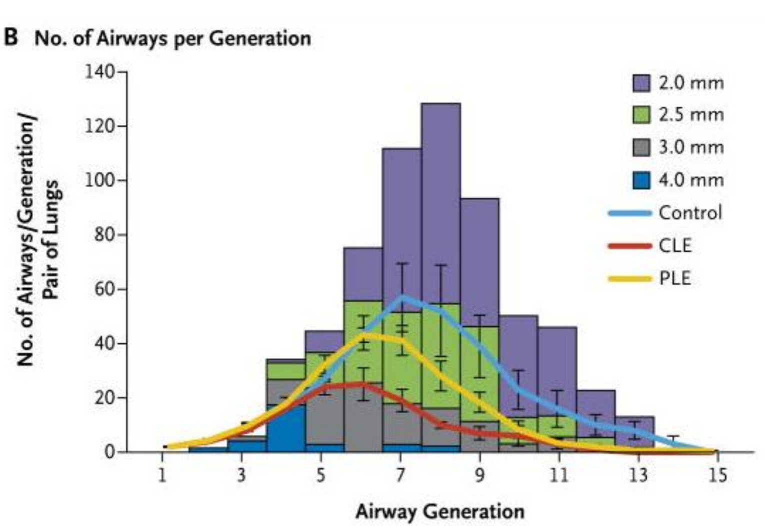
The increase in small airway resistance in COPD could be explained by airway narrowing or airway obliteration.

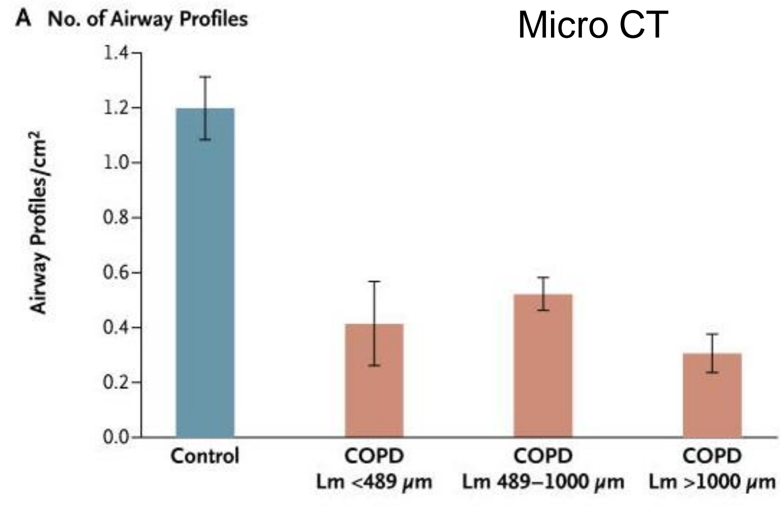
predominantly due to the overall reduction in the diameter of the small airways

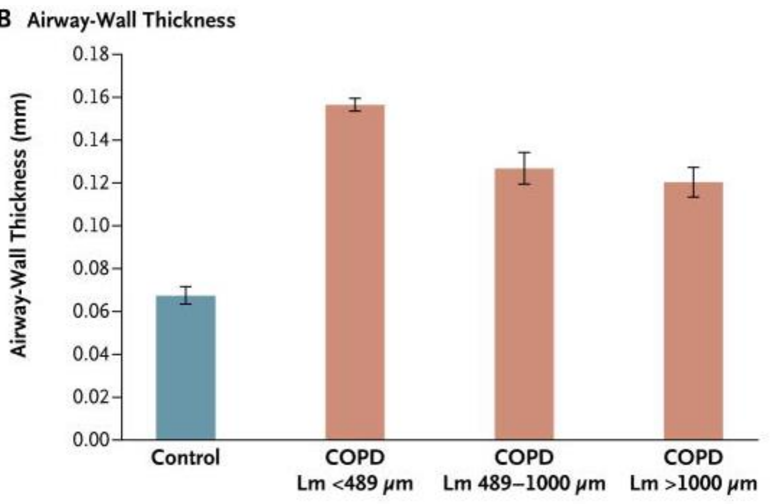
CHEST 2013; 143(5): 1436 – 1443

Pathology studies









N Engl J Med. 2011 Oct 27;365(17):1567-75

Lung physiology

- The measurement of FEV1 by spirometry is not specific for SAD with the larger airways contributing substantially to the expired volume.
- IOS uses sound waves of various frequencies to assess respiratory resistance and reactance during tidal breathing.

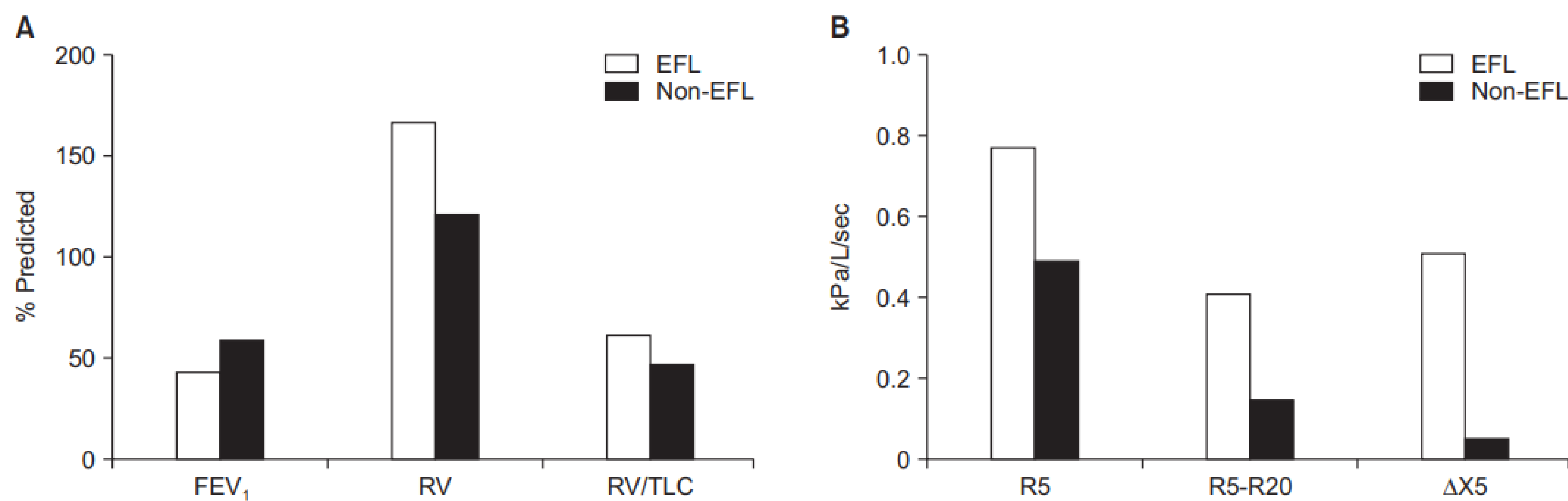
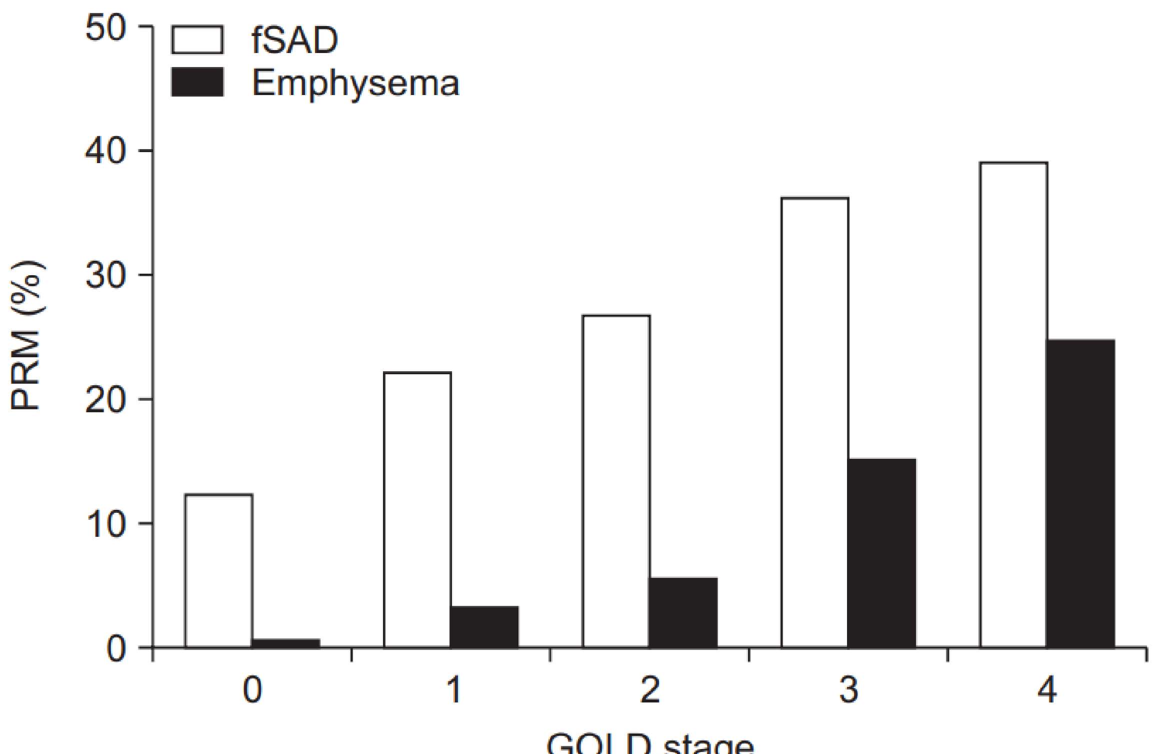


Figure 1. Lung function measurements in chronic obstructive pulmonary disease patients with and without expiratory flow limitation (EFL)[23]. (A) EFL patients have worse airflow obstruction and more hyperinflation measured by residual volume (RV) and total lung capacity (TLC). (B) EFL patients have more impulse oscillometry evidence of small airway disease (R5 and R5–R20). All differences between groups in panels (A) and (B) are statistically significant ($p<0.05$). FEV_1: forced expiratory volume in 1 second.

Tuberc Respir Dis 2017;80:317-324

Imaging studies

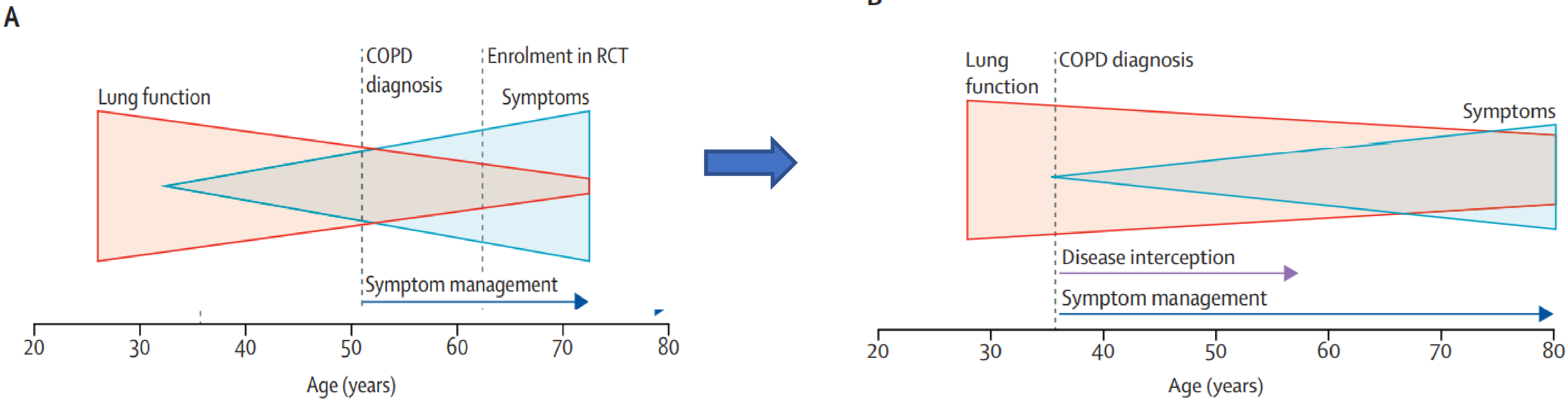
- CT imaging: presence and severity of emphysema
- Emphysema: percentage of voxels <-950 Hounsfield Units (HU) on an inspiratory CT scan
- Gas trapping (d/t SAD or emphysema): percentage of voxels <-856 HU on an expiratory CT scan
- Parametric response mapping (PRM): matches the CT images from inspiratory and expiratory scans to differentiate gas trapping due to emphysema and SAD.



fSAD: functional small airway disease

★ SAD precedes the development of emphysema

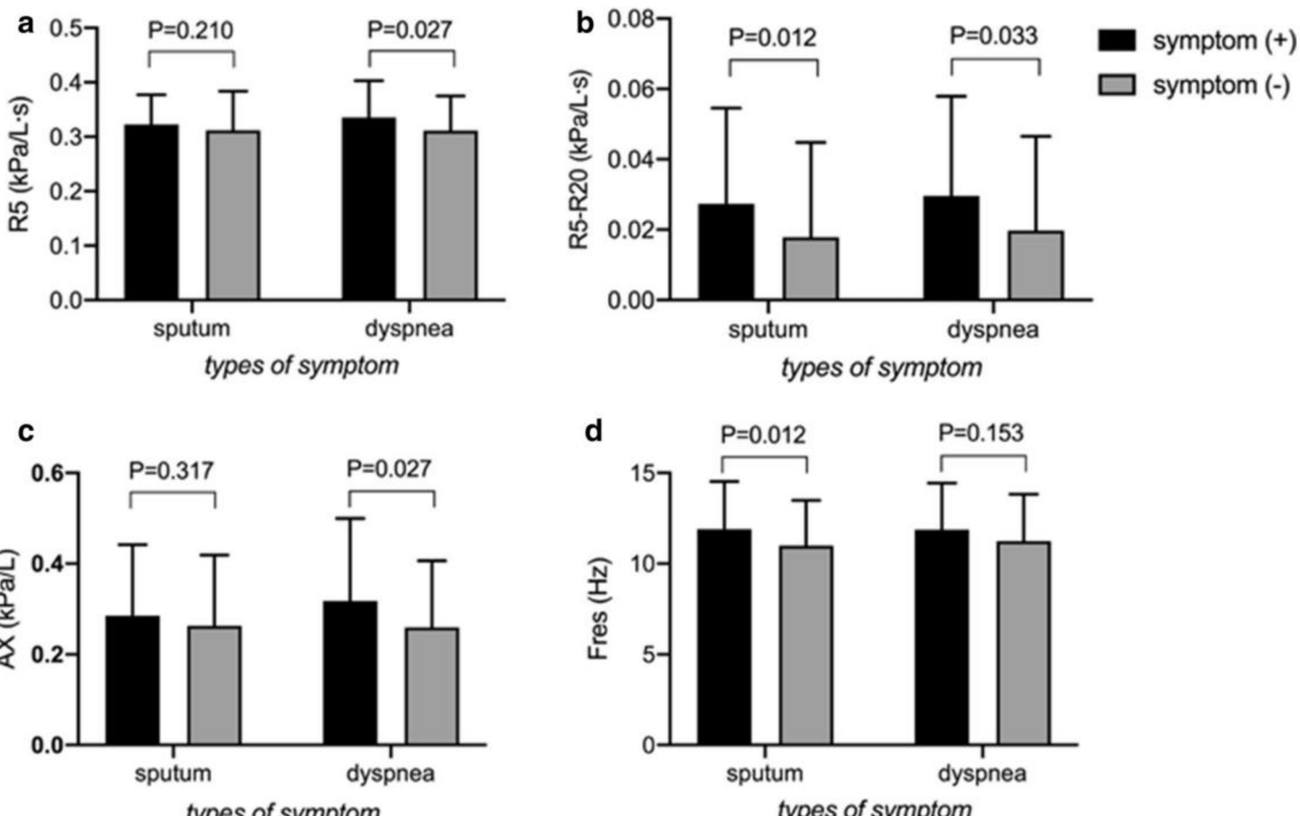
Tuberc Respir Dis 2017;80:317-324



Am J Respir Crit Care Med. 2022 Dec 1;206(11):1317-1325

RESEARCH Open Access

Impulse oscillometry for detection of small airway dysfunction in subjects with chronic respiratory symptoms and preserved pulmonary function



Respir Res. 2021 Feb 24;22(1):68

ORIGINAL ARTICLE

Small Airway Disease in Pre-Chronic Obstructive Pulmonary Disease with Emphysema
A Cross-Sectional Study

Stijn E. Verleden[1,5,6], Jeroen M. H. Hendriks[1,5], Annemiek Snoeckx[2,7], Cindy Mai[7], Yves Mentens[10], Wim Callebaut[11], Bruno De Belie[12], Paul E. Van Schil[1,5], Veronique Verplancke[6], Annelies Janssens[8], Joseph Jacob[13], Ashkan Pakzad[13], Thomas M. Conlon[14], Guney Guvenc[14], Ali Önder Yildirim[14,15], Patrick Pauwels[3,9], Senada Koljenovic[3,9], Johanna M. Kwakkel-Van Erp[4,6], and Thérèse S. Lapperre[4,6]

Rationale: Small airway disease is an important pathophysiological feature of chronic obstructive pulmonary disease (COPD). Recently, “pre-COPD” has been put forward as a potential precursor stage of COPD that is defined by abnormal spirometry findings or significant emphysema on computed tomography (CT) in the absence of airflow obstruction.

Objective: To determine the degree and nature of (small) airway disease in pre-COPD using microCT in a cohort of explant lobes/lungs.

Am J Respir Crit Care Med. 2024 Mar 15;209(6):683-692

Control Pre-COPD Gold stage I Gold stage II Gold stage III/IV

A1 B1 C1 D1 E1

A2 B2 C2 D2 E2

Overview of the computed tomography presentation of the different study groups

Table 2. Summary of *ex vivo* Computed Tomography Scoring

	Control	Pre-COPD	GOLD I	GOLD II	GOLD III/IV	Correlation (*R*) with Second Observer
Emphysema, %	1.3 ± 1.9	22.0 ± 16.9	22.9 ± 16.0	31.3 ± 12.7	85.2 ± 11.2	0.87 (0.75 to 0.93)
Bronchiectasis, %	4.3 ± 4.1	3.5 ± 3.0	4.2 ± 3.6	2.3 ± 1.5	1.7 ± 1.4	0.44 (0.13 to 0.67)
Airway wall thickening, %	4.7 ± 2.8	7.8 ± 6.1	9.7 ± 6.4	5.7 ± 1.9	10.5 ± 3.3	0.22 (−0.12 to 0.51)
Mucus plugging, %	0.0 ± 0.0	1.7 ± 4.4	0.0 ± 0.0	0.5 ± 1.3	1.4 ± 1.3	0.17 (−0.17 to 0.47)
Tree-in-bud changes, %	2.5 ± 7.9	6.1 ± 9.4	4.0 ± 7.6	0.7 ± 1.6	1.4 ± 2.5	0.15 (−0.19 to 0.46)

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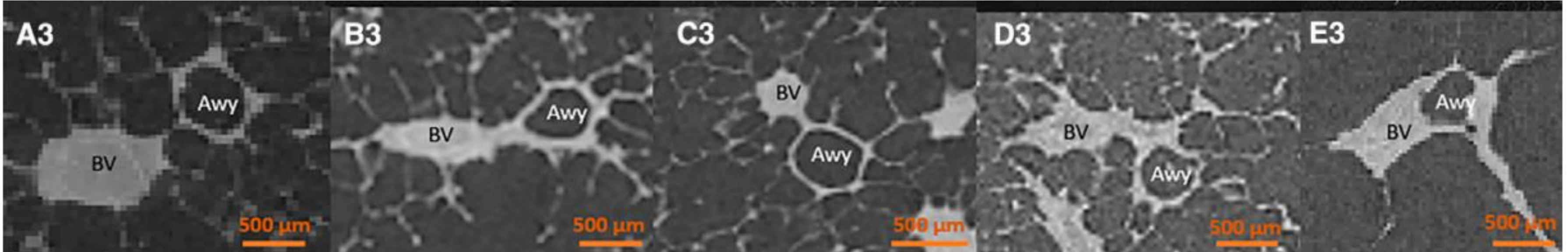
Control | Pre-COPD | Gold stage I | Gold stage II | Gold stage III/IV



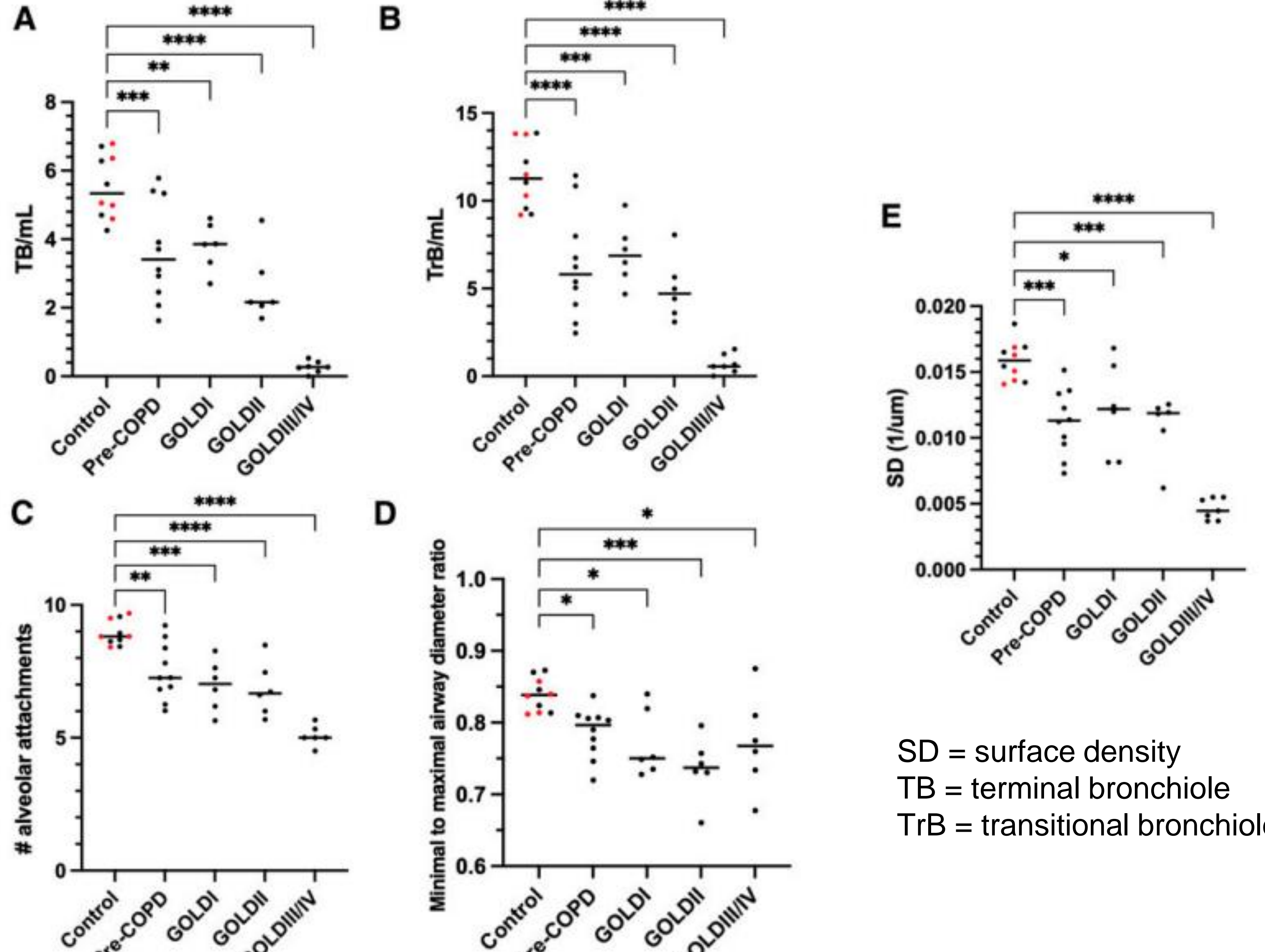
Overview of the micro-computed tomography presentation of the different study groups

Table 3. Summary of MicroCT and Histologic Measures

	Control	Pre-COPD	GOLD I	GOLD II	GOLD III/IV	ANOVA *P* Value
MicroCT measures						
Number of TrBs/mL, *n*	11.45 ± 1.90	6.32 ± 3.03*	6.97 ± 1.75†	5.00 ± 1.77*	0.70 ± 0.54*	<0.0001
Morphometry TrB middle						
Alveolar attachments, *n*	9.2 ± 0.6	7.5 ± 1.0*	7.4 ± 1.0†	7.1 ± 1.0*	4.8 ± 0.8*	<0.0001
Airway wall thickness, µm	52.4 ± 6.2	81.0 ± 15.4	65.5 ± 13.2	85.4 ± 14.1	108 ± 68†	0.0101
Min/max airway diameter	0.86 ± 0.03	0.79 ± 0.03	0.83 ± 0.04	0.77 ± 0.04	0.80 ± 0.17	0.0009
Morphometry TrB end						
Alveolar attachments, *n*	8.9 ± 0.5	7.5 ± 1.1†	7.0 ± 1.0*	6.9 ± 1.0*	5.1 ± 0.4*	<0.0001
Airway wall thickness, µm	53.9 ± 10.6	97.1 ± 39.1‡	68.1 ± 9.7	97.3 ± 19.4‡	82.5 ± 48.6	0.017
Min/max airway diameter	0.84 ± 0.02	0.79 ± 0.03‡	0.77 ± 0.05‡	0.74 ± 0.04*	0.77 ± 0.07‡	0.0007
Number of TBs/mL, *n*	5.53 ± 0.94	3.63 ± 1.47*	3.79 ± 0.70†	2.61 ± 1.05*	0.27 ± 0.17*	<0.0001
Morphometry TB middle						
Alveolar attachments, *n*	10.0 ± 0.7	8.2 ± 1.3‡	7.8 ± 1.2†	7.9 ± 1.1‡	4.8 ± 2.2*	<0.0001
Airway wall thickness, µm	61.5 ± 7.8	97.5 ± 40.0‡	75.3 ± 14.9	98.3 ± 21.1‡	68.2 ± 31.1	0.022
Min/max airway diameter	0.86 ± 0.03	0.81 ± 0.04	0.84 ± 0.03	0.76 ± 0.03‡	0.56 ± 0.20*	<0.0001
Surface density, 1/µm	0.0157 ± 0.0016	0.0117 ± 0.0035*	0.0122 ± 0.0036‡	0.0109 ± 0.0024*	0.0046 ± 0.0008*	<0.0001
Histologic measures						
Chord length, µm	96.3 ± 7.9	132.6 ± 12.1†	164.2 ± 11.9*	170.2 ± 25.0*	314.3 ± 44.9*	<0.0001
Alveolar surface density, 1/µm	0.0112 ± 0.0097	0.080 ± 0.0080‡	0.0747 ± 0.0089‡	0.0715 ± 0.0097†	0.0049.0 ± 0.0117*	<0.0001

TrB = transitional bronchiole; TB = terminal bronchiole

Am J Respir Crit Care Med. 2024 Mar 15;209(6):683-692



SD = surface density
TB = terminal bronchiole
TrB = transitional bronchiole

Am J Respir Crit Care Med. 2024 Mar 15;209(6):683-692

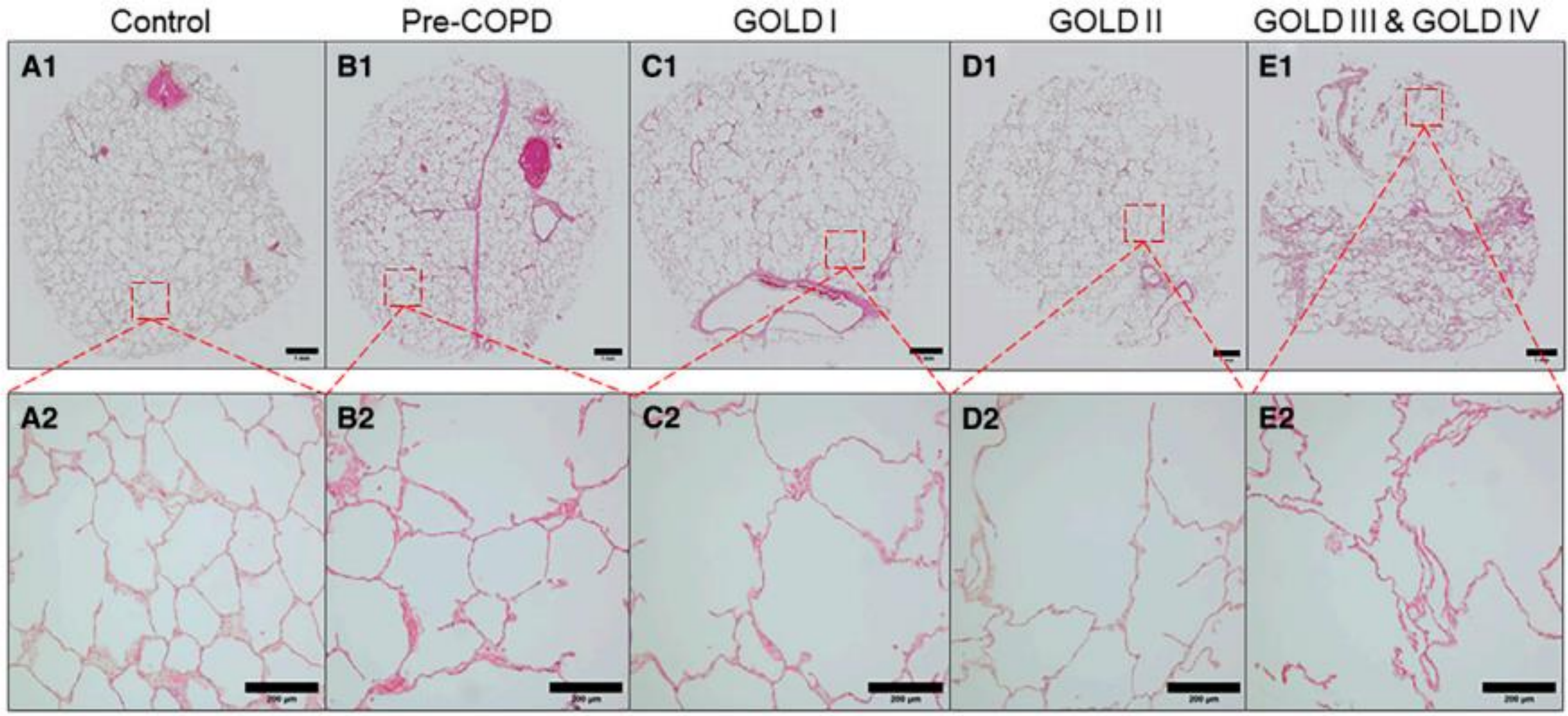
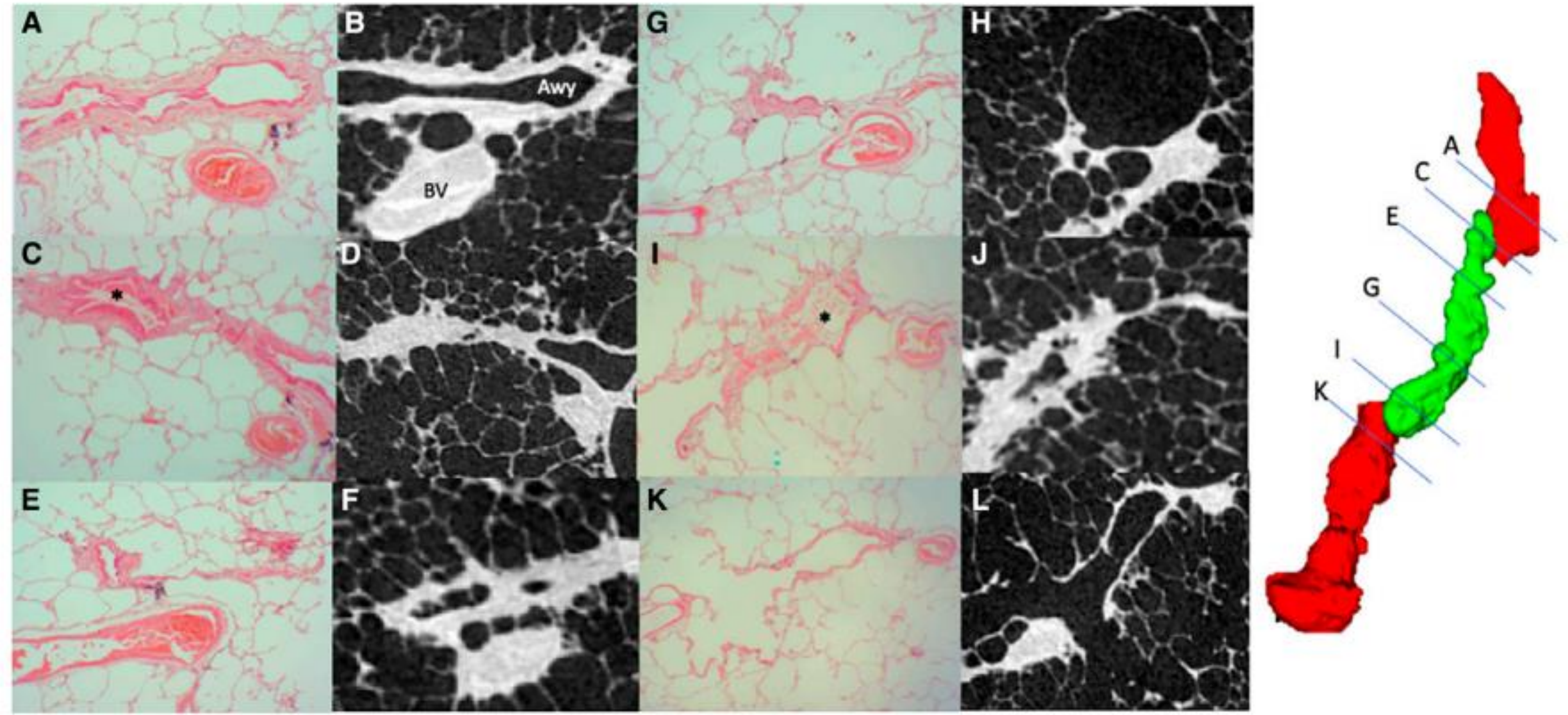


Figure 4. Histopathological correlates of the different study groups. Overview of representative hematoxylin and eosin staining of the cores that were scanned with micro–computed tomography showing inconspicuous parenchyma in controls (*A*) and mild emphysema in pre–chronic obstructive pulmonary disease (COPD) (*B*) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I COPD (*C*), which gets more severe in GOLD stage II COPD (*D*) and GOLD stage III/IV COPD (*E*).

Am J Respir Crit Care Med. 2024 Mar 15;209(6):683-692



Small airway pathology in pre-COPD

Conclusions: Lungs of patients with emphysematous pre-COPD already show fewer small airways and airway remodeling even in the absence of physiologic airway obstruction.

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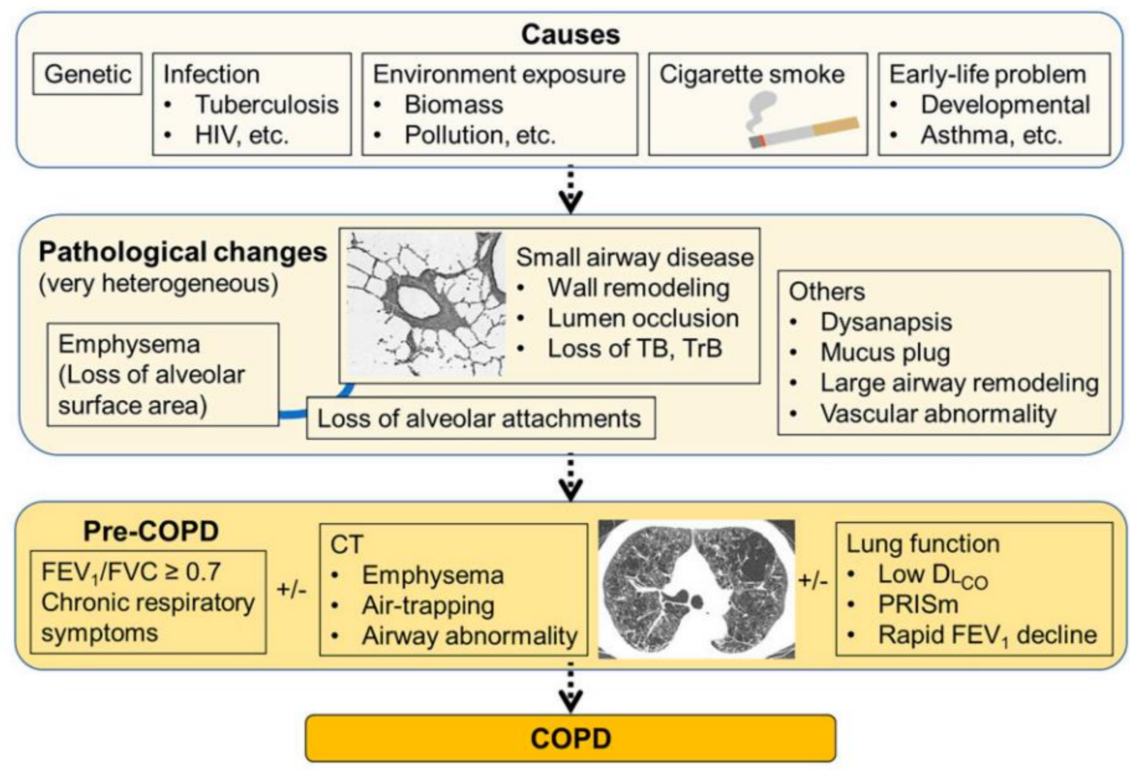
EDITORIALS

Increase Attention to Computed Tomography Findings of Emphysema without Airflow Limitation: Small Airway Disease Is Already There



Am J Respir Crit Care Med. 2024 Mar 15;209(6):619-621

Small airway assessment

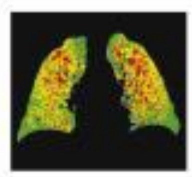
Assessment of lung anatomy

Endobronchial OCT[1]

Allows evaluation of microstructural remodeling in the small airways

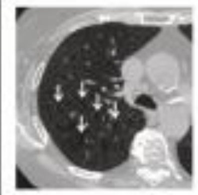
SPECT[2]

Combines emissions from inhaled radiotracer with CT imaging to measure regional ventilation defects



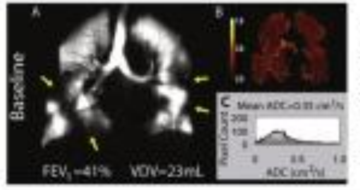
Paired CT-registration-based analysis[3]

Enables examination of paired inspiratory and expiratory CT images using a voxel-wise image analysis technique, for assessing COPD phenotype



MDCT[4]

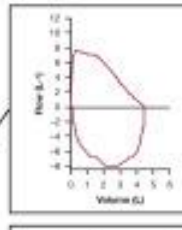
Highly sensitive CT technique able to assess air trapping as a surrogate for small airways disease



Hyperpolarized gas MRI[5]

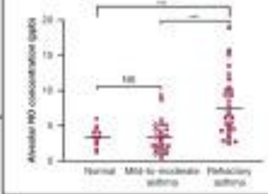
Generates high-resolution images of the airspaces using inhaled hyperpolarized gas

Assessment metrics for whole lung function



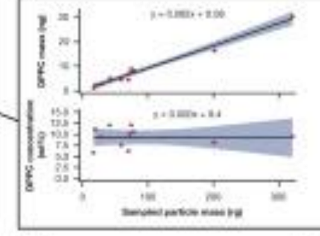
Spirometry[6]

Measures the volume and/or flow of air that can be inhaled and exhaled to identify airway obstruction



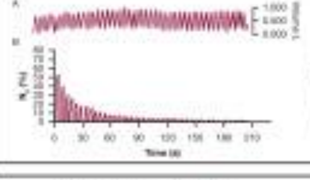
Alveolar fraction of exhaled NO[7]

Exhaled NO concentration is a measure of airway inflammation; models are used to distinguish proximal from alveolar contribution



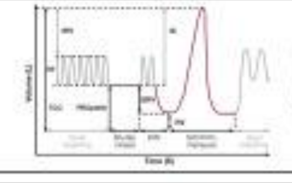
Exhaled particles[8]

Exhaled breath analyzed for the presence and size of specific particles known to be resident in the small airways



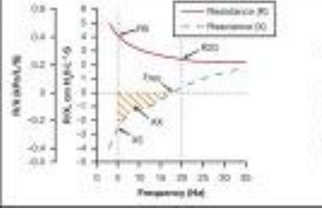
Inert gas washout[9]

Ventilation inhomogeneity measured by assessment of gas washout



Plethysmography[10]

Used to determine static lung volumes and airflow resistance



Oscillometry[11]

Respiratory system impedance measured based on the relationship between pressure and airflow during tidal breathing

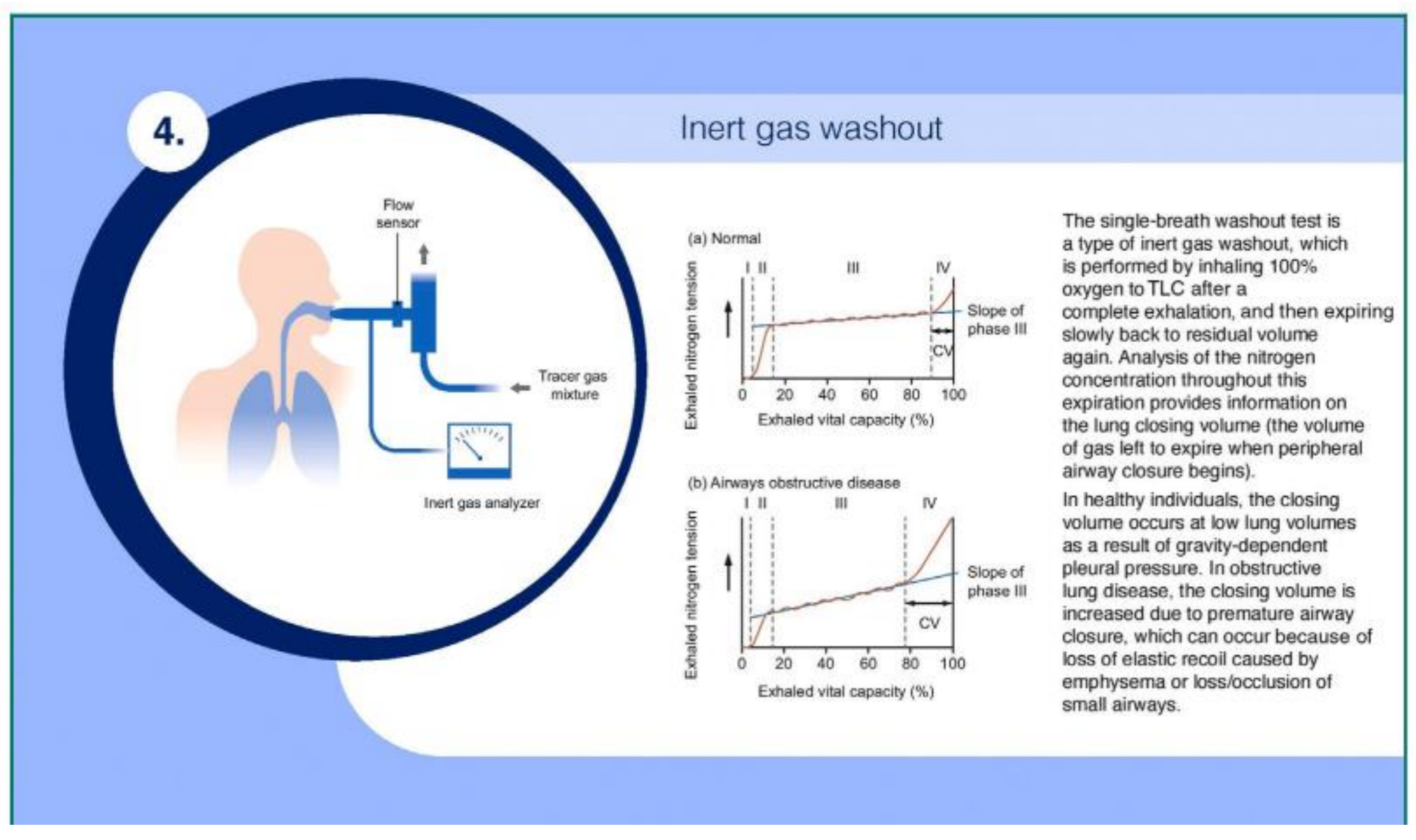
Chest. 2021 Jul;160(1):114-134

- Spirometry
  - ✓ Maximum Mid-Expiratory Flows (FEF 25-75%): poor reproducibility and sensitivity

  Small correlation between MMEF and gas trapping and small airway inflammation
- Plethysmography
  - ✓ Residual volume (RV) and RV/total lung capacity (TLC): assess small airway function, provide accurate information about gas trapping and lung hyperinflation
  - ✓ Small airway dysfunction: RV > 120% of predicted value or RV/TLC >35%
  - ✓ Simple operation, better accuracy, high reproducibility
  - ✓ Not specific to small airways, expensive equipment

- Forced Oscillation Technique and Impulse Oscillometry
  - ✓ simple and noninvasive novel method of lung function assessment
  - ✓ assess small airways.
  - ✓ IOS parameters: total airway resistance (R5)-central airway resistance (R20), peripheral capacitance, resonant frequency (Fres) and reactance area (AX) are significantly correlated with FEF25-75%,
  - ✓ particularly Fres, which is more sensitive than FEF25-75% in the diagnosis of small airway dysfunction
  - ✓ effort-independent

- Gas washout technique



- Gas washout technique
  - ✓ Single breath nitrogen washout (SBNW): reflect the small airway functions of the closed volume (CV), closing capacity (CC) and third phase slope III (SIII)
    - ▪ increase in CV and CC in patients with COPD was related to gas trapping caused by the premature closure of small airways
    - ▪ SIIII is correlated with FEV1%, RV/TLC and diffusion capacity to carbon monoxide (DLCO)
  - ✓ Multiple breath nitrogen washout (MBNW): improvement over the SBNW test
    - ▪ The MBNW test requires a low level of patient cooperation, but it has not been widely used in clinical practice due to the requirement for standardized techniques

- Peripheral Exhaled NO
  - ✓ reflect the level of inflammation in the lung, particularly eosinophilic airway inflammation
  - ✓ At low speed, NO mostly reflects the fractional exhaled NO (FENO) which comes from the central airway, whereas at high speed, it reflects the alveolar concentration of exhaled NO (CANO) which arises from the peripheral airway
  - ✓ Further research is required to determine its value

- Imaging
  - ✓ Ratio of mean lung density between expiratory and inspiratory CT (MLED/I): quantitively evaluate the degree of gas trapping
  - ✓ Parametric response mapping (PRM): small airway dysfunction
  - ✓ Disadvantages: lack of consensus on the best index for small airways disease assessment, and exposure of subjects to ionizing radiation
- Cytology of Induced Sputum

1. High-resolution computed tomography

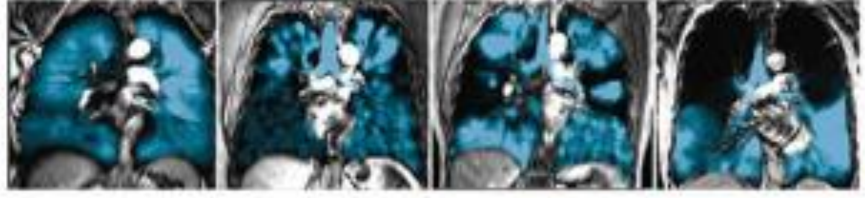
High-resolution computed tomography (HRCT) is a noninvasive imaging technique that can quantify certain features of small airways disease, such as air trapping and ventilation heterogeneity (e.g. during expiration, as observed in the accompanying image).

However, as HRCT can estimate the wall thickness of only those bronchi that are ≥2 mm in diameter the technique does not allow direct assessment of small airway abnormalities, such as airway wall thickening.[a]

2. Hyperpolarized helium magnetic resonance imaging

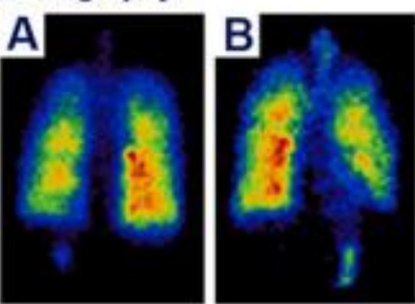
Magnetic resonance imaging (MRI) after the inhalation of hyperpolarized helium or xenon allows the estimation of alveolar size and emphysema and can therefore provide further insight into small airway involvement in COPD.

For example, the accompanying hyperpolarized helium MRI images show progressively poorer ventilation (black areas) with increasing emphysematous destruction of the lungs.[b]



3. Nuclear medicine

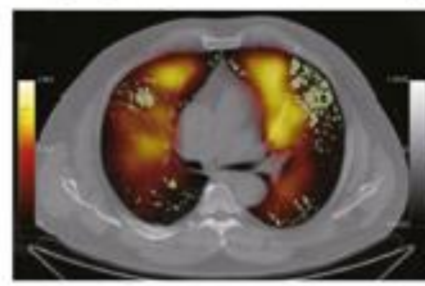
Scintigraphy



Scintigraphy uses radioactive tracers to obtain images of organs and/or record their functioning. It is a powerful tool that has been widely used to visualize and characterize intrapulmonary drug delivery in airways diseases such as asthma and COPD. It allows the measurement of overall lung deposition, and, to some extent, regional deposition (such as the lung periphery).

The accompanying scintigraphic images from a patient with asthma show aerosol deposition of radioactively labeled albuterol particles in the (a) posterior thorax and (b) anterior thorax, which were recorded sequentially, with the patient repositioned between views. Red areas indicate regions of highest radioactivity and black of least radioactivity.[c]

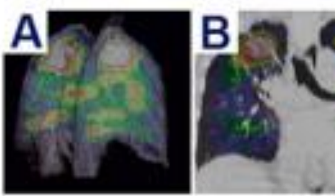
Single-photon emission computed tomography



Single-photon emission computed tomography (SPECT) is a 3-dimensional nuclear imaging technique involving use of radioactive tracers to highlight certain features of organs/tissues, such as the patchy distribution of small airways disease. Single-photon emission computed tomography images are sometimes combined with traditional computed tomography images to correlate functional and structural features.

The accompanying Technegas ventilation SPECT/computed tomography (CT) fusion image shows the axial dimension of a 68-year-old man with moderately severe COPD. It highlights well-ventilated areas of the lung (bright yellow), less-ventilated areas (red), and nonventilated areas (black). Green indicates emphysema. It is apparent that poorly ventilated areas tend to correspond with areas of emphysema.[d]

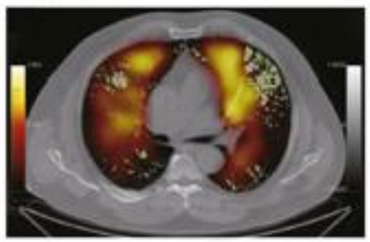
Positron emission tomography



Positron emission tomography (PET), which may also be combined with CT, is another three-dimensional nuclear imaging technique that allows visualization of the regional deposition of radiolabeled tracers. The major difference compared with SPECT is a higher radiation exposure, leading to higher-resolution images.

The accompanying PET images show (a) 3-dimensional and (b) coronal views illustrating the distribution of an inflammatory biomarker, ^{18}fluorodeoxyglucose, predominantly in the upper lungs of a patient with COPD. The range of colors indicate uptake of biomarker, with maximum uptake represented by white and minimum uptake by black.[e]

Single-photon emission computed tomography



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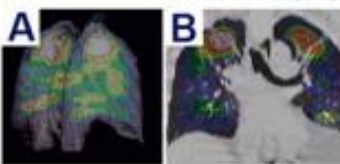
Positron emission tomography



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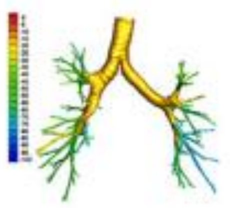
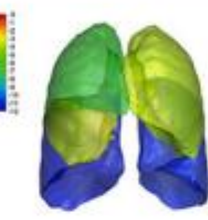
4. Functional respiratory imaging

Functional respiratory imaging combines 3-dimensional computational modeling with imaging techniques to create patient-specific models of lung function.

This can include patient-specific 3-dimensional imaging of airway and lung geometry, defining regional airway resistance as well as patient-specific aerosol deposition patterns. The technique can provide measures of internal airflow distribution, lung volume, lobe volume, airway volume, airway resistance, or lobar perfusion. It can also provide information on aerosol deposition and response to treatment.[f]



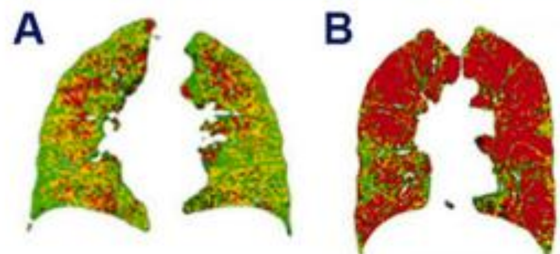
Changes in airway resistance



Changes in lobar hyperinflation

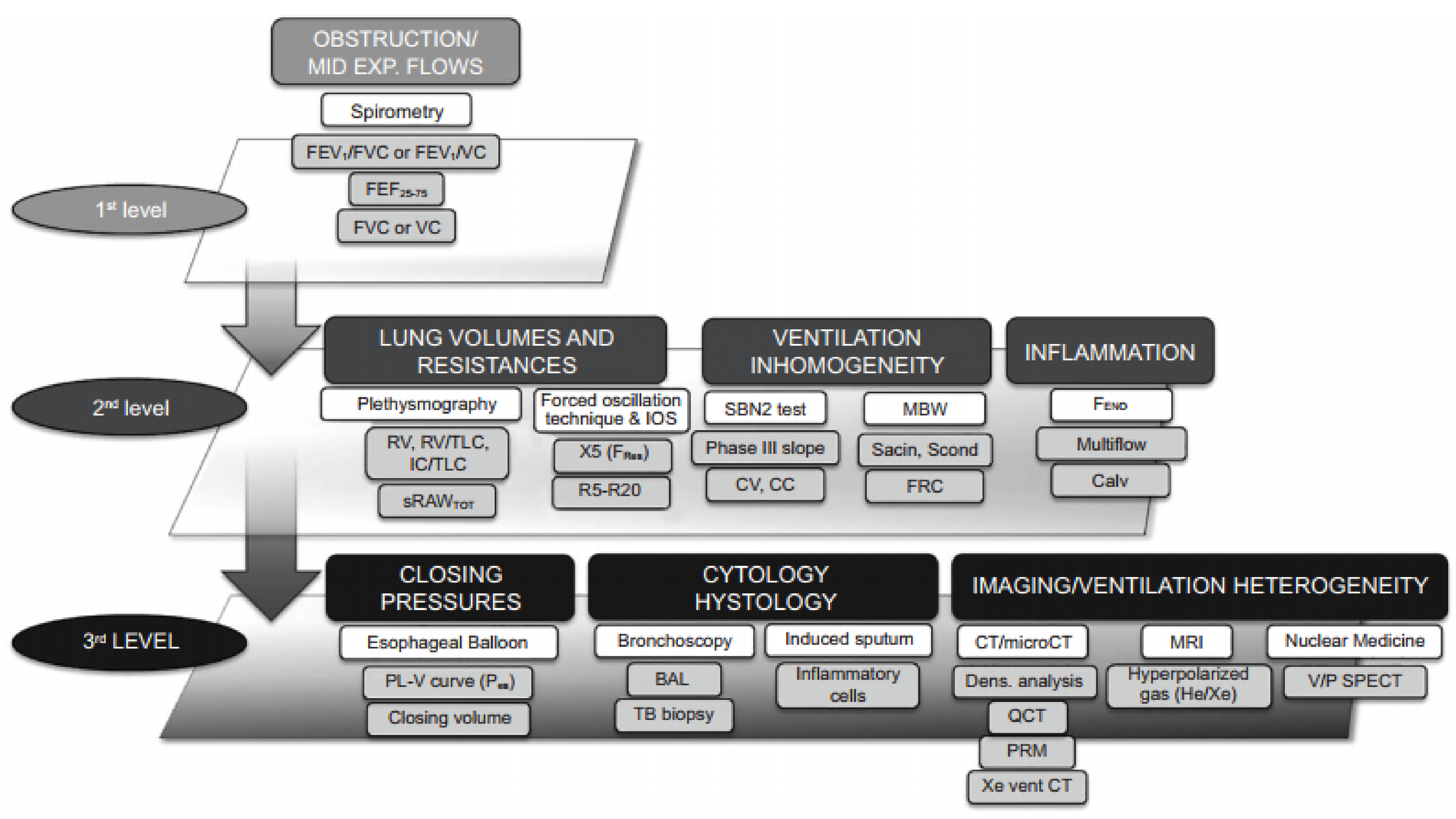
Lobar perfusion

5. Inspiratory/expiratory computed tomography scanning



Inspiratory/expiratory CT scanning is an automated technique providing a quantitative analysis of both large and small airways to help phenotype patients with COPD.

The accompanying images highlight relative volume of normal parenchyma (green), persistent airway disease (red), and functional airway disease (yellow). Case (a) is a patient with predominant conductive airway disease (47% functional and 14% persistent), whereas case (b) is a case with predominant emphysema (25% functional and 55% persistent).[g]



Available noninvasive and invasive assessment tools for small airway assessment.

Respir Care. 2020 Sep;65(9):1392-1412

Table I. Advantages and disadvantages of methods for the assessment of small airway function.

Method	Parameters	Advantages	Disadvantages
Spirometry	FEF50, FEF75%, MMEF, FEV3/FVC, 1-FEV3/FVC, FEV1/FEV6, FEV3/FEV6, FVC/SVC	Noninvasive, easy to perform, highly sensitive, promising	Poor reproducibility and sensitivity, not correlated with inflammation, only reflects the overall function of the lungs, further studies needed
Plethysmography	RV, RV/TLC	Accuracy and reproducibility, correlates well with inflammation	Occupying large area, costly, not widely available
Impulse oscillometry	X5, AX, Fres, R5-R20	Noninvasive, easy to perform, highly sensitive, effort-independent[a]	Not widely available, further studies needed
Single breath nitrogen washout	CV, CC, SIII	Sensitive to early change, good reproducibility and sensitivity	Difficult to perform, not widely available
Multiple breath nitrogen washout	LCI, Scond, Sacin, DLCO	Good reproducibility and sensitivity, effort-independent	Difficult to perform, not widely available
Helium washout test	-	Highly sensitive, good repeatability and reliability	Further studies needed
Exhaled nitric oxide	FeNO, CANO	Noninvasive, easy to perform	Further studies needed
High-resolution computed tomography	MLDE/I, PRM, DPM	Direct imaging of the lungs, easy to perform	Costly, exposure to radiation
Hyperpolarized magnetic resonance imaging	VDS, ADC	Highly sensitive, no risk of radiation exposure	Costly, technically demanding
Intrabronchial optical coherence tomography	-	Direct assessment of the airway structure	Further studies required
Serum markers	Examples: Club cell 16 protein, CXCL8, CX3CL1, PAI-1	Easy to obtain	Further studies required
Induced sputum	Example: Pentosidine	Noninvasive	Further studies required
Bronchoalveolar lavage	Example: MMPs	-	Invasive, further studies required
Bronchoscopy biopsy	-	-	Invasive, rarely used in everyday practice

Exp Ther Med. 2021 Dec;22(6):1386

Treating small airways in COPD

Initial Pharmacological Treatment

Figure 4.2

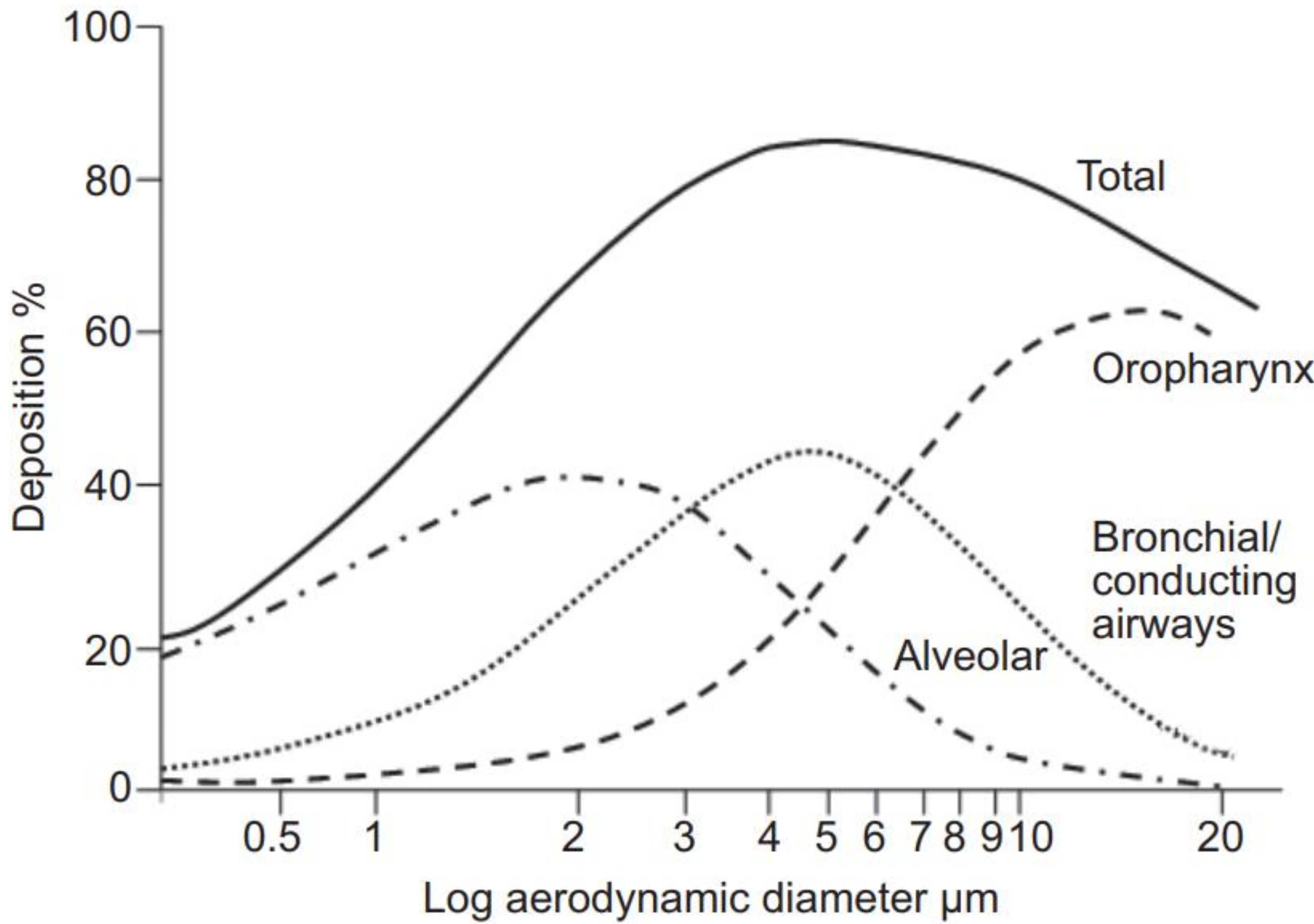
≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	GROUP E **LABA + LAMA*** *consider LABA+LAMA+ICS* if blood eos ≥ 300*	
0 or 1 moderate exacerbations (not leading to hospital admission)	GROUP A **A bronchodilator**	GROUP B **LABA + LAMA***
	mMRC 0-1, CAT < 10	mMRC ≥ 2, CAT ≥ 10

*single inhaler therapy may be more convenient and effective than multiple inhalers

Delivery Systems Targeting Small Airways

- The size of inhaled particles determines their fate within the respiratory tract, with larger particles being deposited in the oropharynx, trachea, and upper bronchial tree, while smaller particles can reach the distal airways.

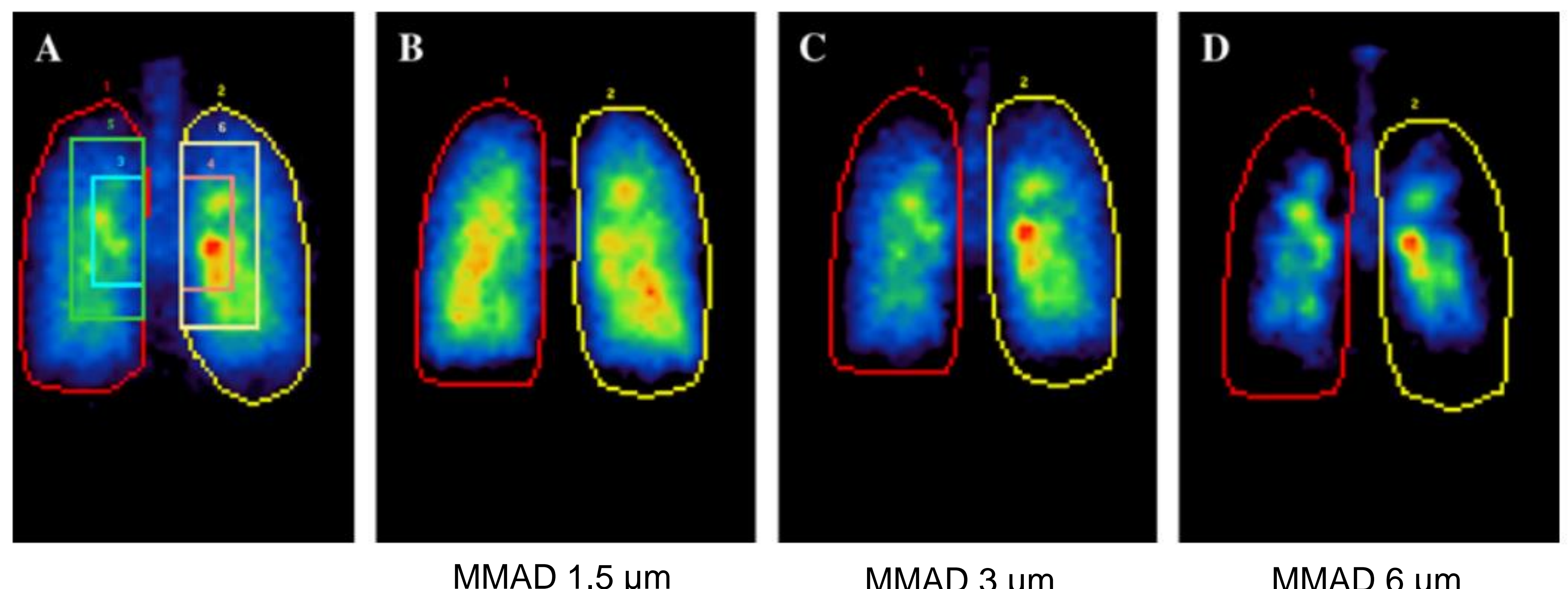
Respiration 2012;84:441–453



For drug delivery to the lower respiratory tract and lungs, particle size (mass-median aerodynamic diameter) can be fine (2-5µm) or extra-fine (< 2µm), which influences the total respirable fraction (particles < 5 µm) and the amount and site of drug deposition (more peripheral deposition with extra-fine particles)

Eur Respir J. 2012 Apr;39(4):1054-5

Effect of MMAD on lung deposition using monodisperse salbutamol



MMAD 1.5 μm   MMAD 3 μm   MMAD 6 μm

TABLE 2. MASS BALANCE AND REGIONAL LUNG DISTRIBUTION

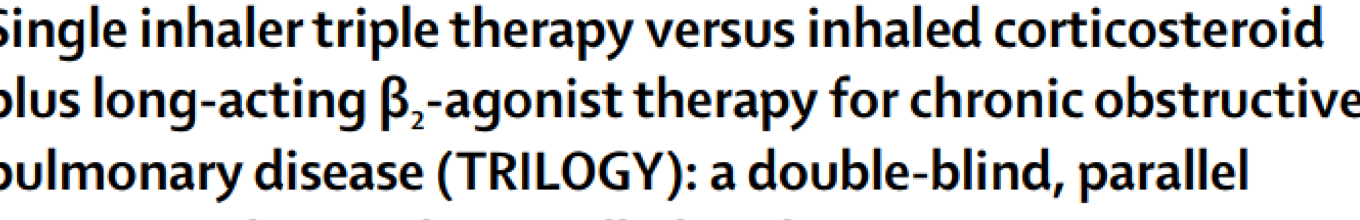
Particle Size (μm)	TLD	OpS	Ex	M	Mp	PI	C+I (%TLD)‡	P (%TLD)	C+I	P
1.5	56.3* ± 9.2	14.6† ± 4.5	21.9† ± 5.7	3.5 ± 1.8	3.8 ± 2.9	0.79† ± 0.14	56.1† ± 6.5	43.9† ± 6.5	31.6 ± 6.3	24.7† ± 5.3
3	51.0 ± 8.9	30.6† ± 7.2	8.3† ± 1.5	4.8 ± 1.4	5.4 ± 3.8	0.60† ± 0.15	65.7† ± 6.4	34.3† ± 6.4	33.8 ± 8.4	17.2† ± 2.6
6	46.0 ± 13.6	42.6† ± 14.6	2.3† ± 0.1	4.8 ± 1.3	4.3 ± 0.9	0.36† ± 0.10	75.4† ± 5.4	24.6† ± 5.4	35.1 ± 11.7	10.9† ± 2.7

Am J Respir Crit Care Med. 2005 Dec 15;172(12):1497-504

Pharmacologic Targeting Small Airways in COPD

- Compared with nonextrafine formulations, the intrapulmonary deposition of extrafine particles studied with the gamma scintigraphy technique, multi-slice CT scans, and computational fluid dynamics in subjects with moderate and severe COPD exhibited better regional lung deposition as well as significant improvements in static lung volumes and a reduction in extrathoracic drug deposition.
- Extrafine triple combination therapy

Respiration 2012;84:441–453



Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial

Dave Singh, Alberto Papi, Massimo Corradi, Ilona Pavlišová, Isabella Montagna, Catherine Francisco, Géraldine Cohuet, Stefano Vezzoli, Mario Scuri, Jørgen Vestbo

Annualised exacerbation rate

BDP/FF/GB (N=687)
BDP/FF (N=680)

	BDP/FF/GB	BDP/FF
Moderate/severe exacerbations	0·45	0·56
Moderate exacerbations	0·33	0·43
Severe exacerbations	0·12	0·14

Probability of having experienced an exacerbation (%)

BDP/FF/GB
BDP/FF

HR 0·80 (95% CI 0·67–0·97); p=0·020

Time since randomisation (weeks)

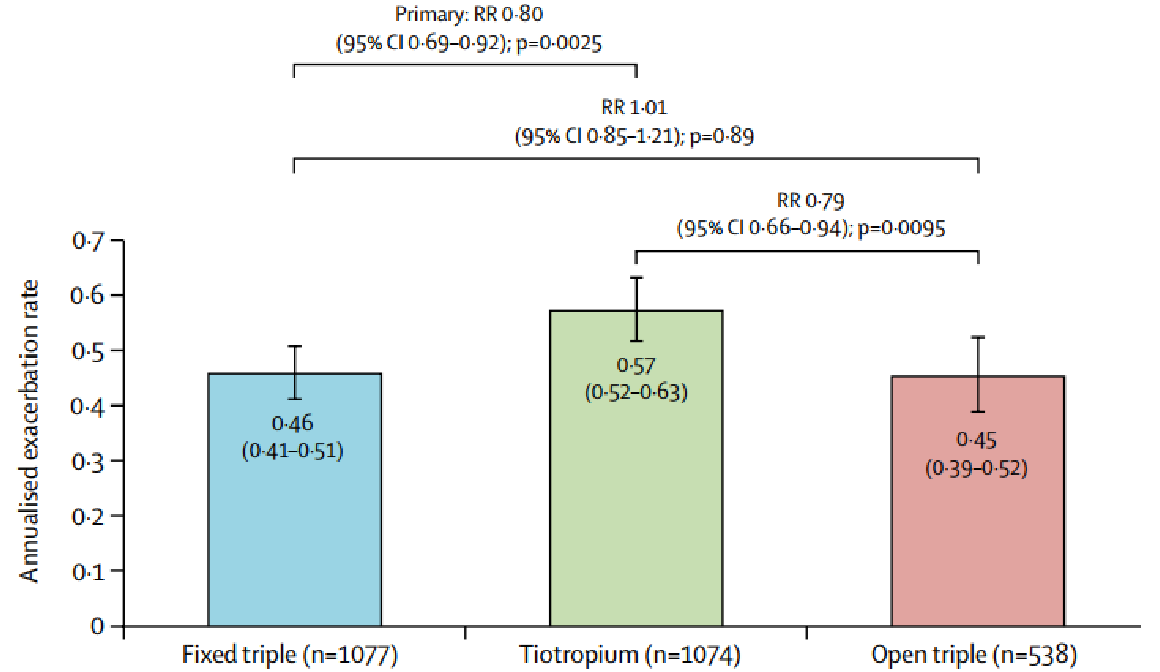
Number at risk	0	4	12	26	40	52
BDP/FF/GB	687	669	620	528	465	292
BDP/FF	680	649	588	483	414	265

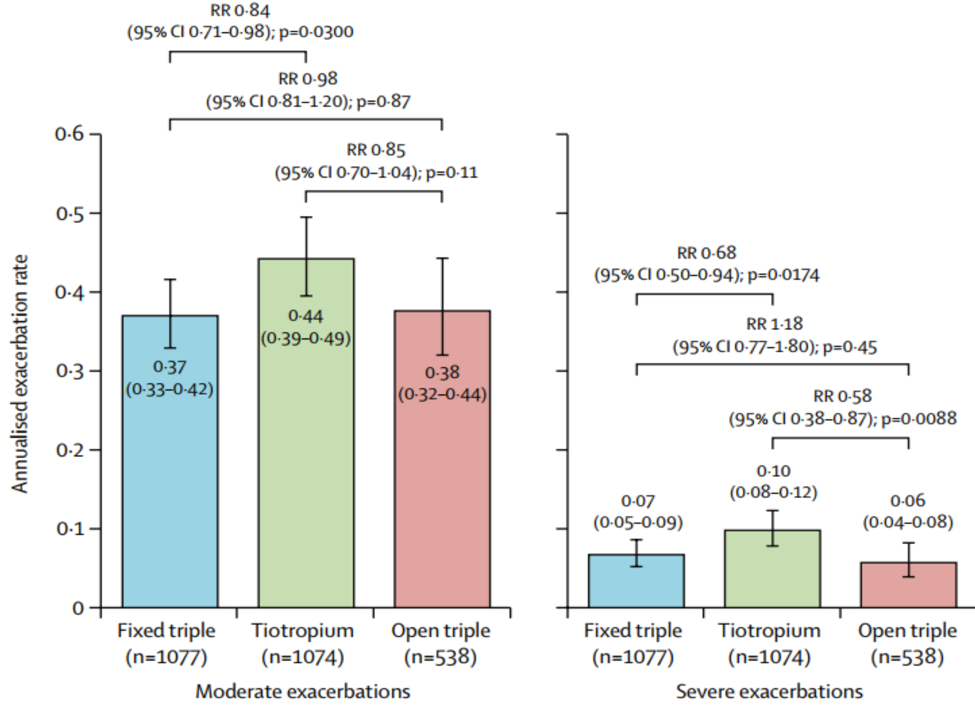
BDP/FF/G, beclometasone diprionate, formoterol fumarate, and glycopyrronium. BDP/FF, beclometasone diprionate and formoterol fumarate

Lancet. 2016 Sep 3;388(10048):963-73

Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial

Jørgen Vestbo, Alberto Papi, Massimo Corradi, Viktor Blazhko, Isabella Montagna, Catherine Francisco, Géraldine Cohuet, Stefano Vezzoli, Mario Scuri, Dave Singh

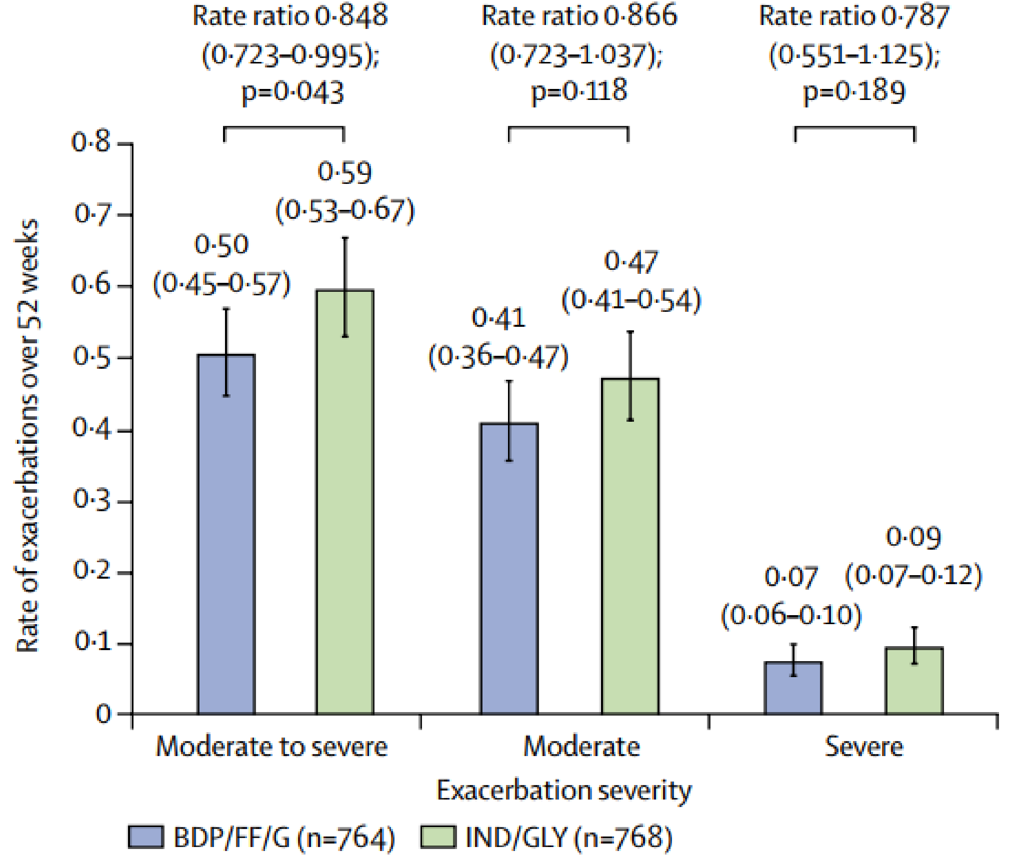


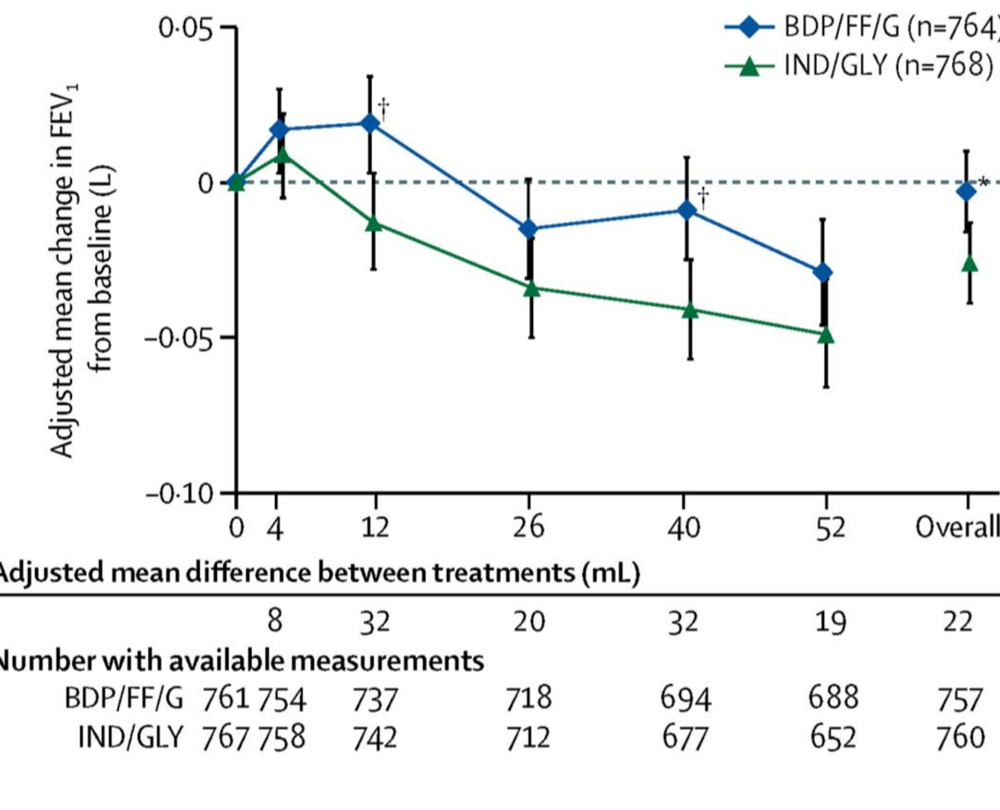


Lancet. 2017 May 13;389(10082):1919-1929

Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial

Alberto Papi, Jørgen Vestbo, Leonardo Fabbri, Massimo Corradi, Hélène Prunier, Géraldine Cohuet, Alessandro Guasconi, Isabella Montagna, Stefano Vezzoli, Stefano Petruzzelli, Mario Scuri, Nicolas Roche*, Dave Singh*

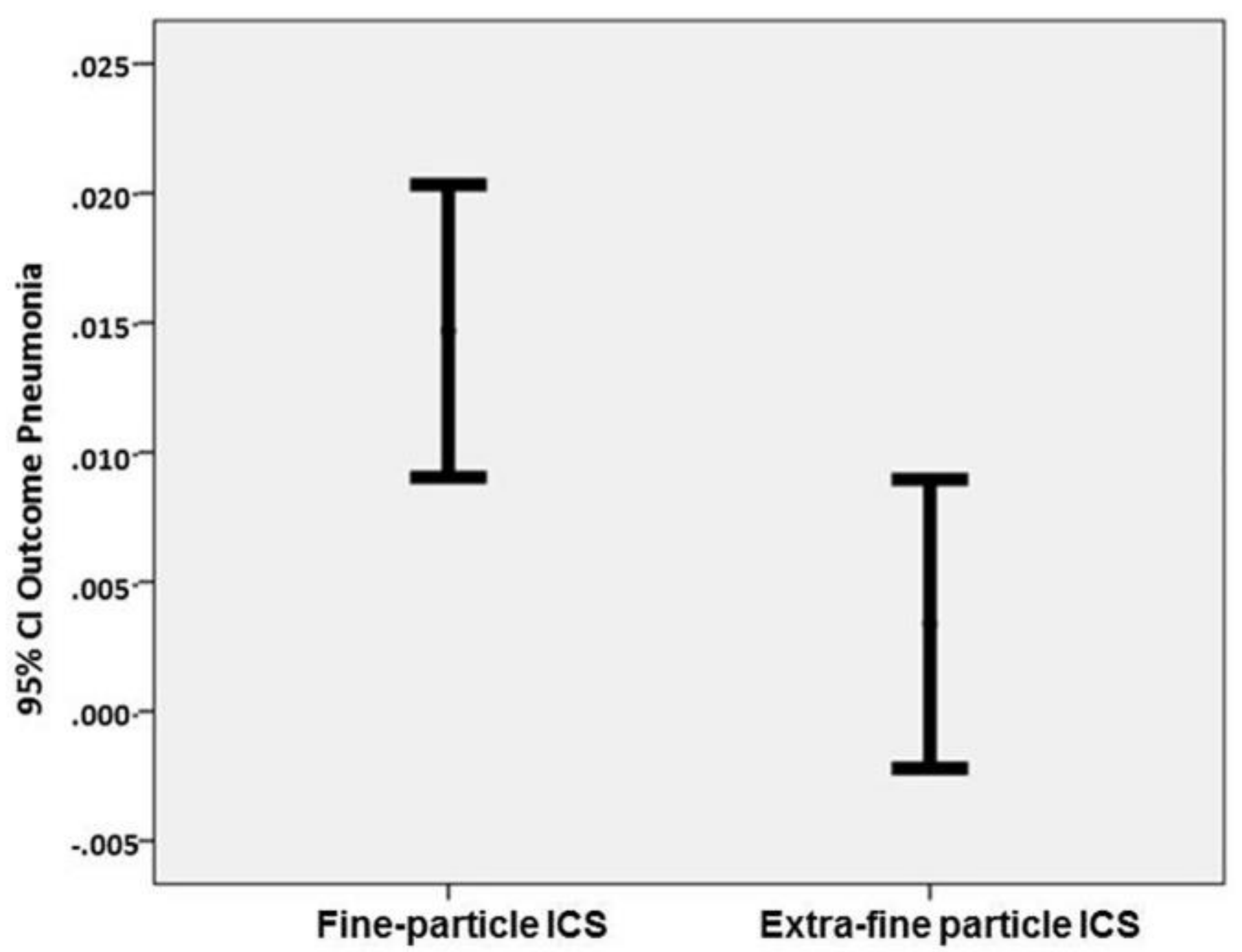




BDP/FF/G, beclometasone diprionate, formoterol fumarate, and glycopyrronium. IND/GLY, indacaterol and glycopyrronium

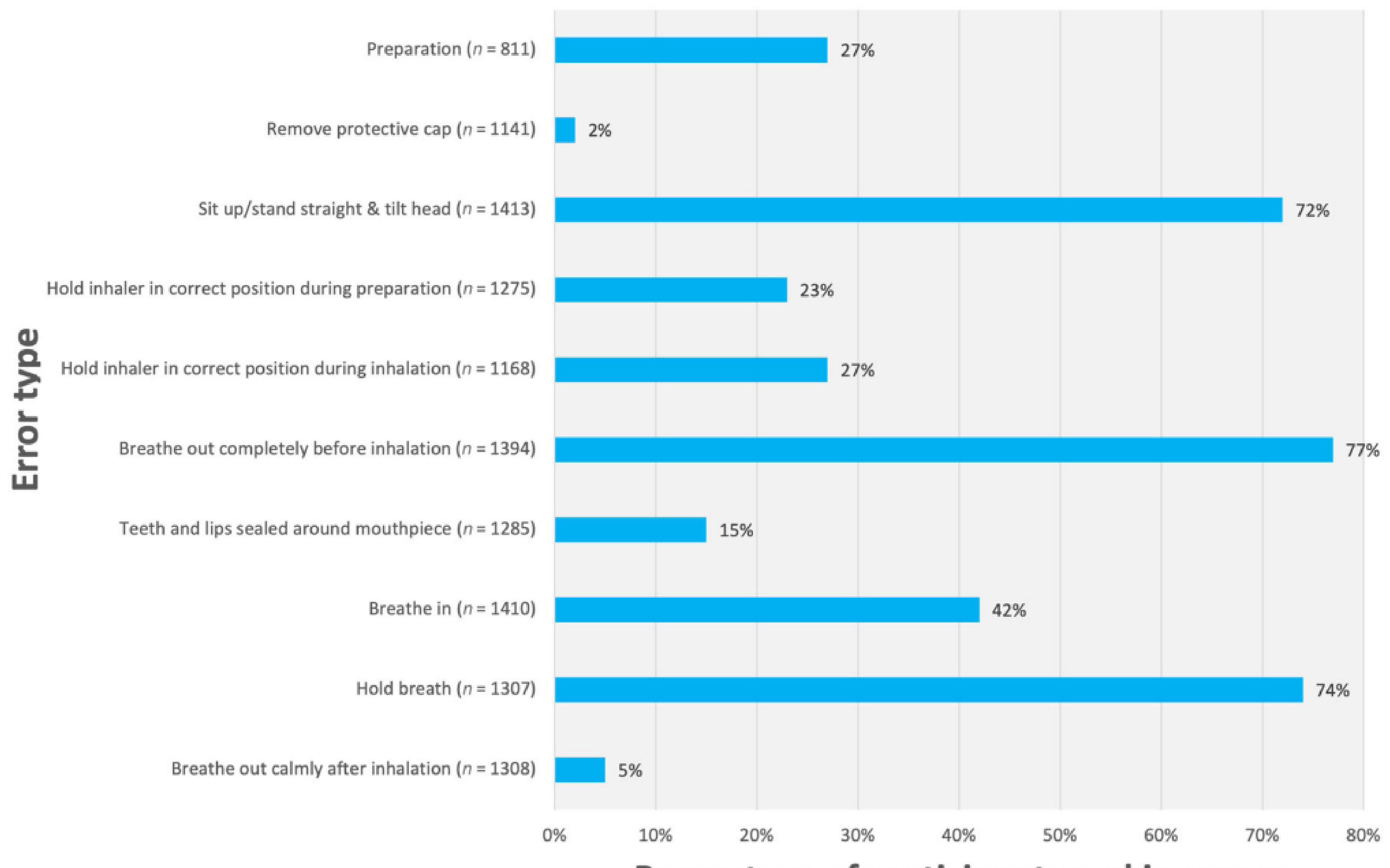
Lancet. 2018 Mar 17;391(10125):1076-1084

Patient on extra-fine particle ICS had lower pneumonia risk than those on fine-particle ICS



PLoS One. 2017 Jun 15;12(6):e0178112

Inspiratory flow, flow acceleration, and inhaled volume are important factors for patients to successfully inhale drug particles from handheld devices into the lower respiratory tract.



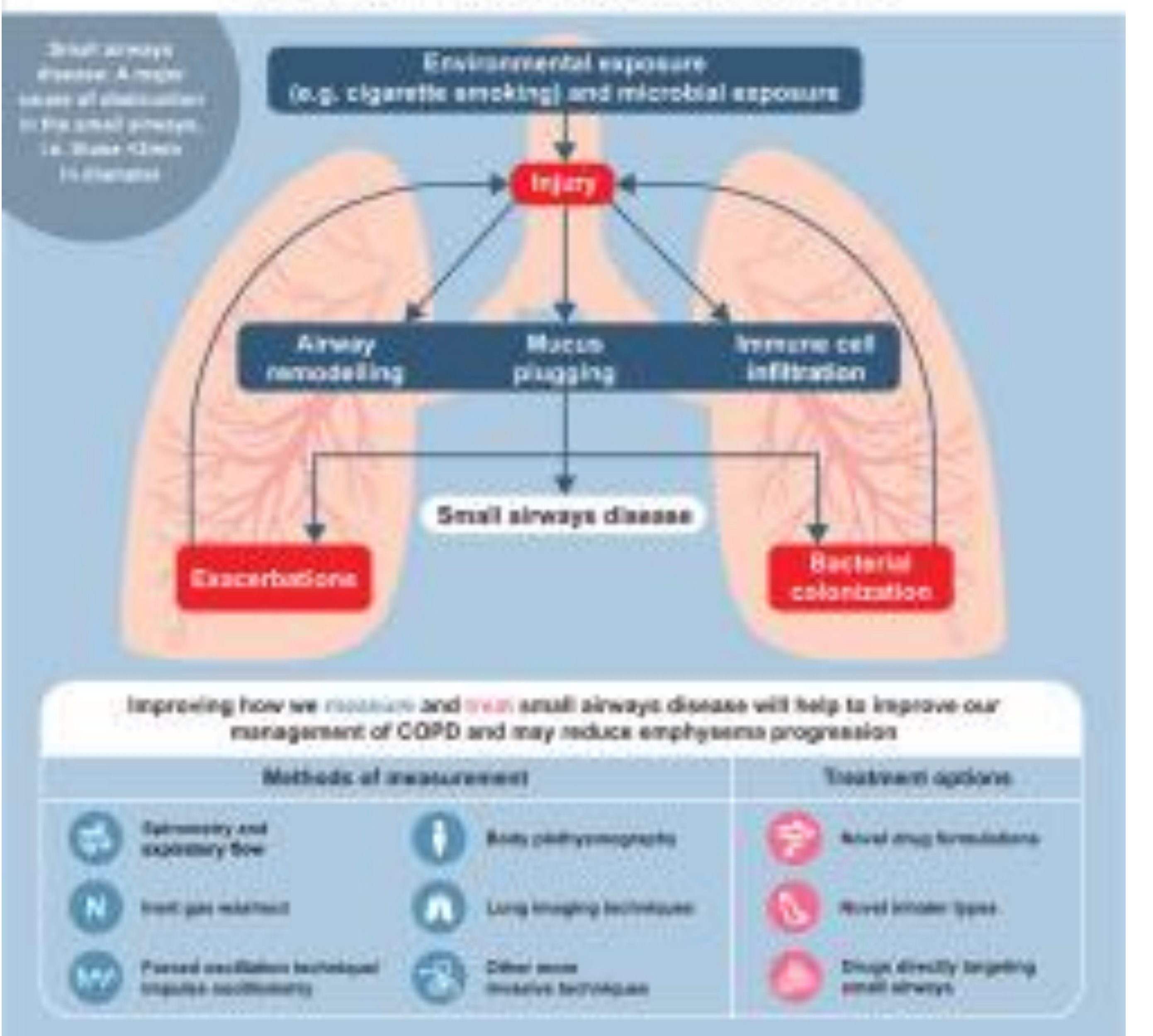
NPJ Prim Care Respir Med. 2022 May 26;32(1):18

TABLE. Therapeutic Options to Target Small Airways Disease

Novel formulations	Mechanism of action
Extrafine particle ICS/LABA formulations[14,57-65] • Beclomethasone dipropionate + formoterol fumarate • Beclomethasone dipropionate + formoterol fumarate + glycopyrronium bromide	• Extrafine particle size enhances delivery to small (as well as large) airways
Co-suspension LAMA/LABA formulation (Bevespi Aerosphere)[66,67] • Glycopyrrolate/formoterol fumarate, formulated using a novel co-suspension delivery technology for administration via MDI	• Co-suspension delivery technology used to formulate glycopyrronium and formoterol fumarate dihydrate together in MDI enables the uniform delivery of both treatments
Extrafine particle ICS[68] • Extrafine beclomethasone	• Extrafine particle size enhances delivery to small (as well as large) airways
Novel inhalers/inhalation systems	**Mechanism of action**
Respimat® Soft Mist™ inhaler[69-73]	• Respimat droplets deposit more uniformly in the different lung regions compared with particles from dry powder inhalers • Respimat exhibited a higher proportion of particles reaching all parts of the lung than did DPIs
Adaptive Aerosol Delivery (AAD®) system[74]	• Adapts to changes in patient's breathing pattern and pulses aerosol during the inspiratory part of the breathing cycle
AKITA® inhalation system[75]	• Uses individualized controlled inhalation to optimize the inhalation maneuver of the patient
Other agents in development	**Mechanism of action**
Inhaled antibiotics[76]	• Combined antimicrobial and anti-inflammatory effects
Alpha-1 antiprotease[77,78]	• Inhibition of proteases involved in the progression of disease
Anti-inflammatory compounds, eg, monoclonal antibodies[79,80]	• Target molecules involved in the inflammatory cascade such as cytokines
Mucolytic agents[81]	• Reduce viscosity of the sputum; antioxidant effects

Conclusion

- Small airway diseases (SAD) is a key pathological feature in COPD.
- Small airway narrowing is the major cause of increased airflow resistance in COPD, and there is evidence that SAD occurs early in the natural history of COPD.
- The narrowing and destruction of small airways appears to precede the development of emphysema.
- Early recognition of SAD and targeted treatment may improve clinical symptoms and delay disease progression.


Small airways disease in COPD
Environmental exposure
(e.g. cigarette smoking) and microbial exposure
Injury
Airway
remodelling
Mucus
plugging
Immune cell
infiltration
Small airways disease
Exacerbations
Bacterial
colonization
Improving how we measure and treat small airways disease will help to improve our
management of COPD and may reduce emphysema progression
Methods of measurement
Treatment options