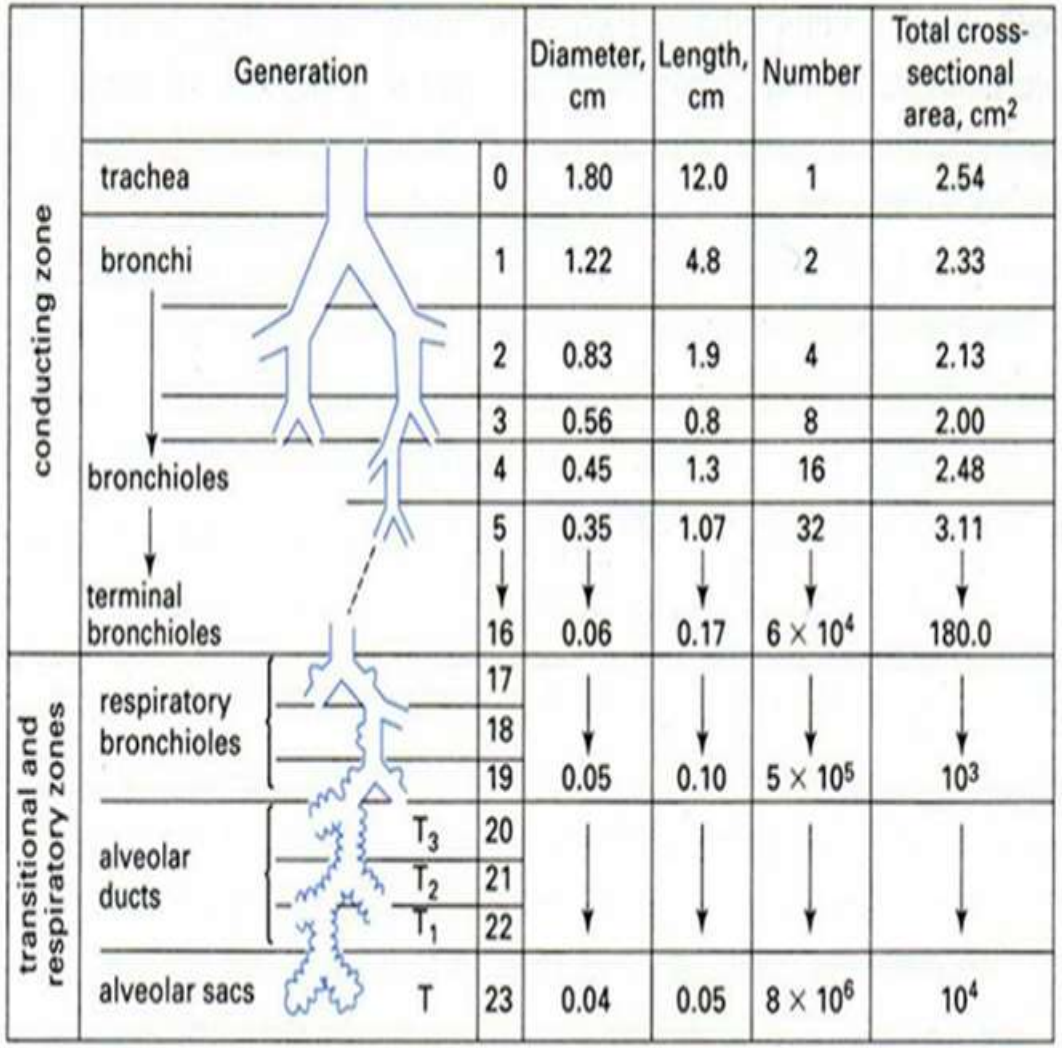
Diagnosis of Small airway diseases

Dr. Sandeep Sharma

Introduction

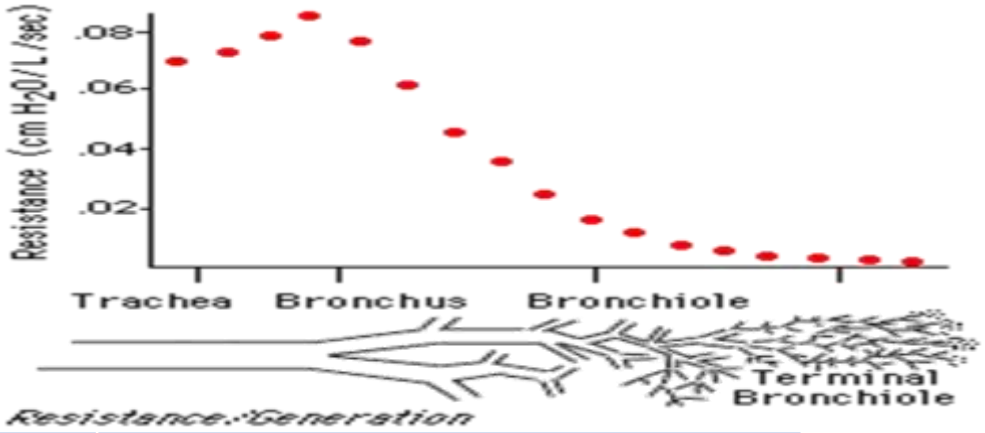
- Airways approximately 23 generations of dichotomously branching tubes from the trachea to the alveoli
- First 15 generations of airways - conducting airways
- Beyond 15 generations - respiratory bronchioles
- Small airways -airways less than 2 mm in diameter



	Generation		Diameter, cm	Length, cm	Number	Total cross-sectional area, cm^2
conducting zone	trachea	0	1.80	12.0	1	2.54
	bronchi	1	1.22	4.8	2	2.33
		2	0.83	1.9	4	2.13
		3	0.56	0.8	8	2.00
	bronchioles	4	0.45	1.3	16	2.48
	terminal bronchioles	5 ↓ 16	0.35 ↓ 0.06	1.07 ↓ 0.17	32 ↓ 6×10^4	3.11 ↓ 180.0
transitional and respiratory zones	respiratory bronchioles	17 18 19	↓ 0.05	↓ 0.10	↓ 5×10^5	↓ 10^3
	alveolar ducts	T_3 20 T_2 21 T_1 22	↓	↓	↓	↓
	alveolar sacs	T 23	0.04	0.05	8×10^6	10^4

Weibel ER , et al.Lab Invest. 1963; 12: 131 55

Small vs large airways



	Large Airways	Small Airways
Cross sectional area	Lesser	Greater
Flow	Turbulent	Laminar
Resistant affected by density	Yes	No
Cartilaginous support	+	-
Lined by surfactant	-	+

Ranga V et al., Arch Pathol Lab Med. 1978; 102: 60917

Zone of silence / quiet zone of lung

- Small contributions to airway resistance about 10 % (1)
- Obstruction of 75% of all small airways is required before changes can be detected by routine pulmonary function tests (2)
- Collateral channels-vital capacity unimpaired
- Small airway can undergo considerable damage before the either dynamic or static lung function become abnormal

1. Macklem PT. Am J Respir Crit Care Med. Vol 157. pp S181–S183 1998
2.Cosio M, et al. N Engl J Med 1978; 298: 1277–1281

Why is it important?

- Early diagnosis and treatment is needed to prevent disease progression

Small airway diseases

- Small airways disease (bronchiolitis) may be classified according to its clinical setting ,its histologic pattern, or on the basis of HRCT imaging findings.
- The clinical classification is on the basis of the proven or presumed etiology, or on associated systemic conditions
- No single classification scheme for bronchiolar diseases has been widely accepted

Small airways obstruction

Small airways obstruction may lead to

- A reduction in airflow
- Increased airways resistance
- Gas trapping
- Inhomogeneity of ventilation

Diagnostic methods

Pulmonary function test	Imaging	Invasive
• Spirometry • Plethysmography • Oscillometry • Inert gas washout • Exhaled nitric oxide test	• High resolution CT • Hyperpolarised helium MRI • 2D gamma scintigraphy • SPECT • PET	• Lung biopsy

Spirometry

- In health, the main site of airways resistance is the 4^{th}-8^{th} airway generations
- FEV1 largely reflects large airways obstruction
- Forced Expiratory Flow between 25 and 75% of the FVC (FEF25-75)- latter part of the vital capacity - affected by increased resistance in small airways as lung volume decreases (1)
- FEF25-75 measures airflow during effort independent part of FVC
- FEF25-75 is dependent on the FVC & patient effort
- If FEF25-75 is not adjusted for lung volume, there is poor reproducibility(2)

1)McFadden ER Jr, Linden DA et al., Am J Med. 1972 Jun;52(6):725-37

2)Boggs PB , et al . Ann Allergy. 1982; 48: 1378. 39.

Spirometry

- FVC & FEV1 normal and abnormal FEF25-75
- Forced Expiratory Volume in 3 sec (FEV3) to FVC ratio -an alternative measure of small airways disease
- The fraction of air not expired in the first 3 sec (**1-FEV3/FVC**) is - estimate the growing proportion of long time constant lung units
- As FEV1/FVC falls, the FEV3/ FVC falls and the 1-FEV3/FVC rises
- A fall in FVC suggests small airway closure and gas trapping

Original Article

FEF_{25-75}% Is a More Sensitive Measure Reflecting Airway Dysfunction in Patients with Asthma: A Comparison Study Using FEF_{25-75}% and FEV_1%

Rundong Qin, MD[a,*], Jiaying An, MD[b,*], Jiaxing Xie, PhD[a,*], Renbin Huang, MD[a], Yanqing Xie, PhD[b], Li He, MD[a], Hui Xv, MD[b], Geng Qian, MD[b], and Jing Li, MD[a] *Guangdong, Guangdong, P.R. China*

BACKGROUND: Reduced forced expiratory flow between 25% and 75% of vital capacity percent predicted (FEF_{25-75}%) representing small airway dysfunction (SAD) was associated with asthma development and progression.

OBJECTIVE: To investigate whether FEF_{25-75}% was superior to forced expiratory volume in 1 second in predicted (FEV_1%) in reflecting asthma features in adult patients.

METHODS: A retrospective spirometry dataset comprising 1801 adult patients with confirmed asthma and a subgroup of 332 patients having detailed clinical data were used to explore the association of FEF_{25-75}% and/or FEV_1% with clinical features of asthma.

RESULTS: Of the 1801 subjects, FEV_1% and FEF_{25-75}% ranged from 136.8% to 10.2% and 127.3% to 3.1%, respectively. FEF_{25-75}% < 65% was present in 1,478 (82.07%) of patients. FEF_{25-75}% was strongly correlated with matched FEV_1% ($r = 0.900$, $P < .001$). FEF_{25-75}% and FEV_1% were both correlated with airway hyperresponsiveness ($r = 0.436$, $P < .001$; $r = 0.367$, $P < .001$), asthma control test score ($r = 0.329$, $P < .001$; $r = 0.335$, $P < .001$), and sputum eosinophil count ($r = -0.306$, $P < .001$; $r = -0.307$, $P < .001$). Receiver-operating characteristic curves showed that FEF_{25-75}% had greater value in predicting severe asthma (area under the curve: 0.84 vs 0.81, $P = .018$), airflow obstruction (0.97 vs 0.89, $P < .001$), and severe bronchial hyperresponsiveness (0.74 vs 0.69, $P = .012$) as compared with FEV_1%. Patients with SAD (FEF_{25-75}% < 65%) in the presence of normal FEV_1% exhibited higher sputum eosinophil counts and had an increased dosage of daily inhaled corticosteroids ($P < .001$ and $P = .010$) than patients with normal lung function and their FEF_{25-75}% values correlated with sputum eosinophil count ($r = -0.419$, $P = .015$), but not FEV_1%.

CONCLUSION: FEF_{25-75}% represented small airway function and was more sensitive at reflecting airway hyperresponsiveness, inflammation, and disease severity as compared with FEV_1% in patients with asthma. Our data suggest further assessment of

Qin R et al. An J J Allergy Clin Immunol Pract. 2021 Oct;9(10):3649-3659.e6.

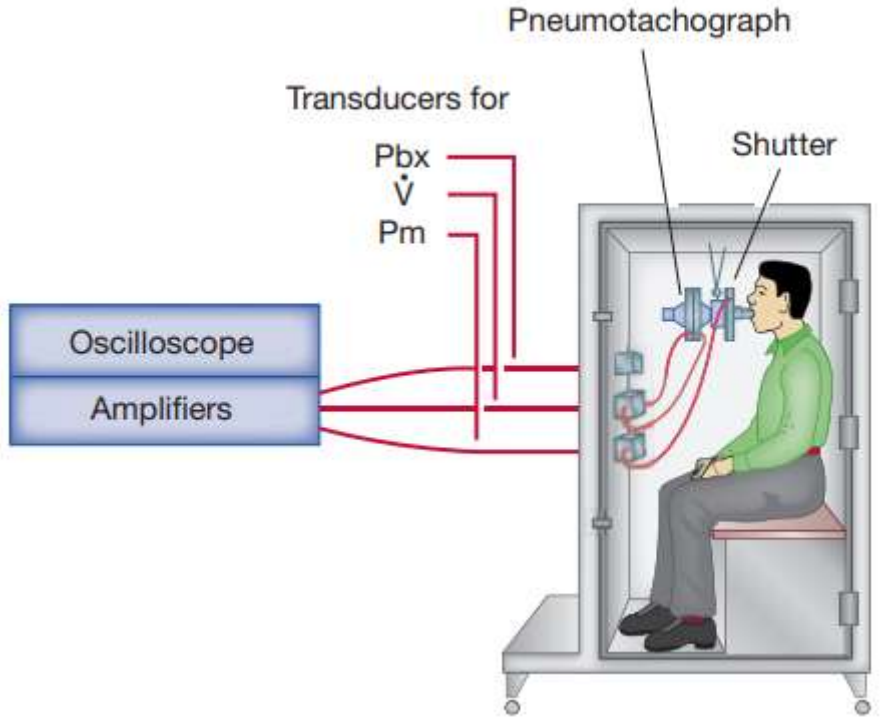
Spirometry

- Not specific to small airways changes
- Relatively insensitive to early disease and subtle changes
- FEF25-75, as it is frequently normal if the FEV1/FVC ratio is 75%
- Effort dependent
- FEF25%–75% is less reproducible and also correlate poorly with air trapping or histologic evidence of small airway inflammation

Gelb AF, et al., Chest J. 1983; 84: 4734

Body Plethysmography

- Derived from the Greek plethysmos, meaning “enlargement.”
- DuBois and coworkers introduce a practical plethysmographic technique, based on Boyle’s law.
- **P1V1=P2V2**
- 3 types of body plethysmographs
  (1) Pressure plethysmograph
  (2) Volume plethysmograph
  (3) Pressure-corrected flow plethysmograph



Plethysmography

- Measure of gas trapping and lung hyperinflation
- It is a function of airflow limitation, lung elastic recoil, and chest wall compliance.
- Airway narrowing results in a prolonged time constant for expiration-gas trapping
- RV - measure of small airways dysfunction and may be raised before the onset of abnormal spirometry
- RV/TLC ratio -marker of gas trapping as the TLC is frequently raised in obstructive lung disease
- Airways resistance (Raw) -measured by assessing pressure and flow at the mouth during body

Pellegrino R.et al. Eur Respir J. 2005; 26: 94868.

Small airway impairment in moderate to severe asthmatics without significant proximal airway obstruction

Table 3 Small airway obstruction in patients without proximal airway obstruction.

	SAO, $n = 115$		No SAO, $n = 82$
	N (%[a])	Value % (±SD)	Value % (±SD)
Hyperinflation			
FRC > 120% pred	45 (49.5%)	151 (±34)	94 (±15)
RV > pred + 1.64 RSD	68 (59.1%)	174 (±46)	93 (±27)
RV/TLC > pred + 1.64 RSD	52 (45.2%)	152 (±26)	93 (±22)
Airflow limitation			
FEF_{25-75} < pred − 1.64 RSD	27 (24.1%)	54 (±11)	83 (±22)
FEF_{50} < pred − 1.64 RSD	17 (15.0%)	46 (±11)	81 (±23)
Expiratory trapping			
SVC − FVC > 10%	21 (18.8%)	0.66 (±0.37)	0.03 (±0.25)

The residual volume (RV) is an important measure of small airways dysfunction and may be raised before the onset of abnormal spirometry in asthma *Respir Med. 2013; 107: 166774.*

Airway Inflammation in Severe Chronic Obstructive Pulmonary Disease

Relationship with Lung Function and Radiologic Emphysema

Graziella Turato, Renzo Zuin, Massimo Miniati, Simonetta Baraldo, Federico Rea, Bianca Beghé, Simonetta Monti, Bruno Formichi, Piera Boschetto, Sergio Harari, Alberto Papi, Piero Maestrelli, Leonardo M. Fabbri, and Marina Saetta

The lung pathology of severe chronic obstructive pulmonary disease (COPD) has been poorly investigated. We examined surgical specimens obtained from patients with severe (forced expiratory volume in 1 second [FEV_1] = 29 ± 3% predicted, n = 9) or mild/no airflow limitation (FEV_1 = 86 ± 5% predicted, n = 9) and similar smoking history. With histochemical and immunohistochemical methods we quantified the structural changes and the inflammatory cells in small airways and in muscular pulmonary arteries. As compared with smokers with mild/no COPD, smokers with severe COPD had an increased number of leukocytes in the small airways, which showed a positive correlation with the radiologic score of emphysema and with the value of residual volume, and a negative correlation with the values of FEV_1 and carbon monoxide diffusing capacity. The inflammatory process was characterized by an increase in $CD8^+$ and $CD4^+$ T-lymphocytes in the airway wall and by an increase in macrophages in the airway epithelium. When all smokers were considered together, the smoking history was correlated with both the airway wall and smooth muscle thickness, suggesting that smoking itself may play a role in the development of structural changes. No structural and cellular differences were observed in pulmonary arteries between smokers with severe COPD and smokers with mild/no COPD. In conclusion, in the small airways of smokers with severe COPD, there is an increased number of leukocytes, which is correlated with reduced expiratory flow, lung hyperinflation, carbon monoxide diffusion impairment, and radiologic emphysema, suggesting a role for this inflammatory response in the clinical progression of the disease.

TABLE 1. PATIENT CHARACTERISTICS*

	Severe COPD	Mild/No COPD	p
Patients examined†, n	9	9	
Age, yr	63 ± 3	60 ± 2	NS
Sex†, M/F	6/3	8/1	
Smoking history, pack-yr	49 ± 10	43 ± 6	NS
FEV_1, % predicted	29 ± 3	86 ± 5	< 0.0001
FEV_1/FVC, %	32 ± 2	68 ± 2	< 0.0001
TLC, % predicted	114 ± 6	95 ± 6	< 0.05
FRC, % predicted	144 ± 9	98 ± 7	< 0.005
RV, % predicted	163 ± 13	94 ± 10	< 0.001
D_{LCO}, % predicted	29 ± 4	77 ± 10	< 0.001
Kco, % predicted	30 ± 5	82 ± 11	< 0.005
Pa_{O_2}, mm Hg	65 ± 6	83 ± 2	< 0.05
Pa_{CO_2}, mm Hg	41 ± 2	40 ± 1	NS
Emphysema score‡	9 (7–15)	4 (0–5)	< 0.001

RV correlates with the degree of inflammatory changes in small airways in COPD

Am J Respir Crit Care Med Vol 166. pp 105–110, 2002

Distal Lung Dysfunction at Night in Nocturnal Asthma

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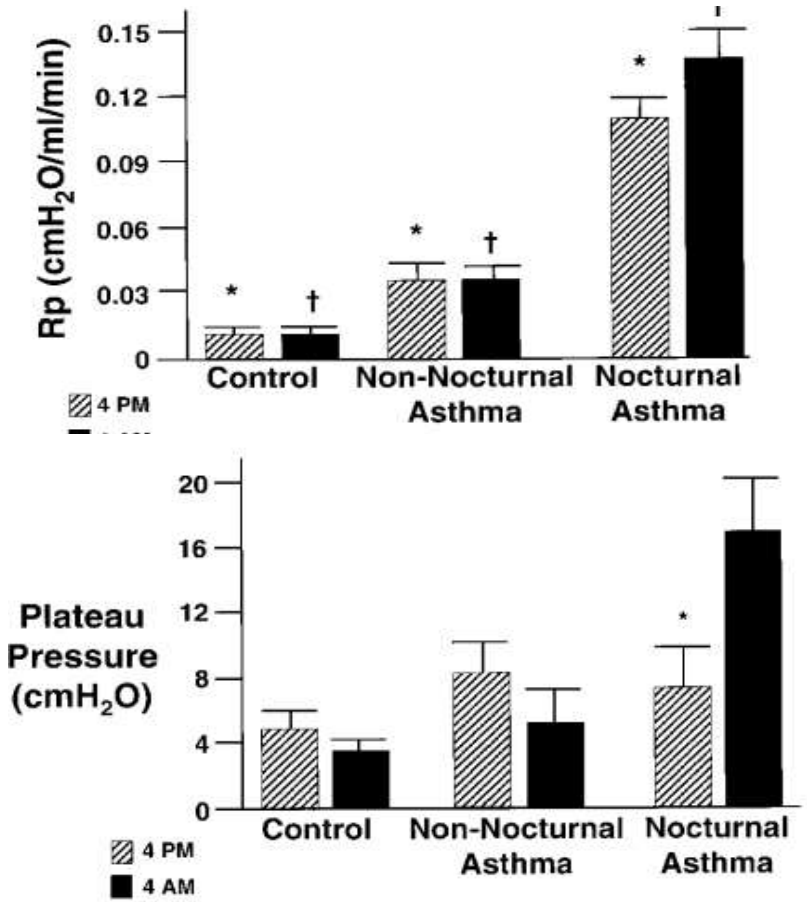
Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado Health Sciences Center, National Jewish Medical and Research Center, Denver, Colorado; and Division of Pulmonary Disease and Critical Care Medicine, University of Vermont College of Medicine, Burlington, Vermont

We have previously shown that patients with nocturnal worsening of asthma (nocturnal asthma) exhibit increased parenchymal inflammation at night. To evaluate the functional significance of this parenchymal inflammation, 10 subjects with nocturnal asthma (NA), four subjects with non-nocturnal asthma (NNA), and four normal control subjects underwent bronchoscopy with measurement of peripheral airways resistance (Rp) at 4:00 P.M. and at 4:00 A.M. Employing a wedged bronchoscope technique, Rp was measured. Flow was stopped, and the pressure reached after 10 s of decay was termed the plateau pressure. The time constant of this decay (τ) was measured, and the peripheral compliance (Cp) was calculated as τ/Rp. The NA group exhibited the highest Rp values at 4:00 P.M. and at 4:00 A.M. as compared with the NNA and control groups, but all groups were significantly different from each other at 4:00 P.M.: NA, 0.113 ± 0.02 cm H_2O/ml/min; NNA, 0.033 ± 0.005 cm H_2O/ml/min; Control subjects, 0.010 ± 0.001 cm H_2O/ml/min; $p = 0.0001$; and at 4:00 A.M.: NA, 0.129 ± 0.023 cm H_2O/ml/min; NNA, 0.035 ± 0.007 cm H_2O/ml/min; Control subjects, 0.009 ± 0.002 cm H_2O/ml/min; $p = 0.0003$. None of the groups exhibited statistically significant differences in Rp between 4:00 P.M. and 4:00 A.M.. The plateau pressure increased significantly from 4:00 P.M. to 4:00 A.M., but only in the NA group (7.7 ± 0.9 cm H_2O at 4:00 P.M. versus 16.9 ± 4.6 cm H_2O at 4:00 A.M.; $p = 0.0004$). Cp was decreased in the NA group as compared with the NNA and control groups at both 4:00 P.M. ($p = 0.0003$) and 4:00 A.M. ($p = 0.003$). The Rp positively correlated with the residual volume at both 4:00 P.M. ($r = 0.71$, $p = 0.004$) and 4:00 A.M. ($r = 0.59$, $p = 0.03$). We conclude that the distal lung units, specifically the collateral channels, and may be functionally altered at night in NA.



Am J Respir Crit Care Med Vol 163. pp 1551–1556, 2001

TABLE 2. LUNG VOLUME AND SPECIFIC CONDUCTANCE

	Non-Asthma Control Subjects	Subjects with Non-Nocturnal Asthma	Subjects with Nocturnal Asthma	p Values
4:00 P.M. Vtg, L	3.3 ± 0.2	2.8 ± 0.3	4.1 ± 0.2	0.003 (NA > NNA,C)
4:00 P.M. Vtg, % pred	92.2 ± 6.1	83.5 ± 3.0	116.0 ± 7.5	0.01 (NA > NNA)
4:00 A.M. Vtg, L	3.3 ± 0.3	3.1 ± 0.4	4.5 ± 0.3	0.02 (NA > NNA)
4:00 A.M. Vtg, % pred	95.7 ± 12.3	92.2 ± 1.9	125.3 ± 11.1	0.07
4:00 P.M. TLC, L	6.4 ± 0.4	6.0 ± 0.7	7.4 ± 0.3	0.10
4:00 P.M. TLC, % pred	99.2 ± 2.5	96.5 ± 0.5	115.8 ± 4.3	0.004 (NA > NNA,C)
4:00 A.M. TLC, L	6.5 ± 0.3	6.3 ± 0.9	7.5 ± 0.3	0.20
4:00 A.M. TLC, % pred	102.0 ± 3.3	100.2 ± 4.5	117.7 ± 4.5	0.02 (NA > NNA,C)
4:00 P.M. RV, L	1.7 ± 0.1	1.5 ± 0.2	2.8 ± 0.2	0.0009 (NA > NNA,C)
4:00 P.M. RV, %	124.5 ± 14.5	112.3 ± 12.4	197.2 ± 20.6	0.01 (NA > NNA,C)
4:00 A.M. RV, L	1.7 ± 0.2	1.6 ± 0.3	3.0 ± 0.3	0.005 (NA > NNA,C)
4:00 A.M. RV, %	127.3 ± 17.3	119.2 ± 12.6	208.3 ± 25.8	0.02 (NA > NNA,C)
4:00 P.M. sGaw, L/S/cm H_2O/L	0.17 ± 0.02	0.17 ± 0.04	0.10 ± 0.02	0.12
4:00 P.M. sGaw, % pred	96.2 ± 12.4	83.7 ± 13.9	61.2 ± 17.6	0.32
4:00 A.M. sGaw, L/S/cm H_2O/L	0.13 ± 0.01	0.14 ± 0.03	0.07 ± 0.01	0.04 (NA < NNA,C)
4:00 A.M. sGaw, % pred	74.3 ± 12.7	69.7 ± 11.2	43.8 ± 9.2	0.14

The RV correlates with the degree of inflammatory changes in small airways with peripheral airway resistance in asthma

Am J Respir Crit Care Med Vol 163. pp 1551–1556, 2001

Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation

Ronald L. Sorkness,[1] Eugene R. Bleecker,[2] William W. Busse,[1] William J. Calhoun,[3,4] Mario Castro,[5]

population, or a severe asthma phenotype. We hypothesized that severe asthma has a characteristic physiology of airway obstruction, and we evaluated spirometry, lung volumes, and reversibility during a stable interval in 287 severe and 382 nonsevere asthma subjects from the National Heart, Lung, and Blood Institute Severe Asthma Research Program. We partitioned airway obstruction into components of air trapping [indicated by forced vital capacity (FVC)] and airflow limitation [indicated by forced expiratory volume in 1 s (FEV_1)/FVC]. Severe asthma had prominent air trapping, evident as reduced FVC over the entire range of FEV_1/FVC. This pattern was confirmed with measures of residual lung volume/total lung capacity (TLC) in a subgroup. In contrast, nonsevere asthma did not exhibit prominent air trapping, even at FEV_1/FVC <75% predicted. Air trapping also was associated with increases in TLC and functional reserve capacity. After maximal bronchodilation, FEV_1 reversed similarly from baseline in severe and nonsevere asthma, but the severe asthma classification was an independent predictor of residual reduction in FEV_1 after maximal bronchodilation. An increase in FVC accounted for most of the reversal of FEV_1 when baseline FEV_1 was <60% predicted. We conclude that air trapping is a characteristic feature of the severe asthma population, suggesting that there is a pathological process associated with severe asthma that makes airways more vulnerable to this component.

	Group		
	No asthma	Nonsevere asthma	Severe asthma
Demographics			
n	85	382	287
%Female sex	65	71	67
Age	32±10.1	34±11.6	43±12.9*
Age of asthma onset	NA	15±13.0	17±15.6
Years asthma duration	NA	20±12.7	26±14.1*
Baseline spirometry‡			
n	85	382	287
FEV_1, %Predicted	102±10.6	84±16.8†	61±22.0*†
FVC, %Predicted	103±11.6	94±15.3†	75±19.2*†
(FEV_1/FVC), %Predicted	99±7.1	89±11.3†	79±15.4*†
FEF_{25-75}, %Predicted	101±23.2	67±26.9†	42±28.8*†
PEF, %Predicted	103±18.3	88±19.7†	67±23.7*†
Lung volumes‡			
n	20	75	84
TLC, %Predicted	107±11.3	108±12.7	112±18.9
RV, %Predicted	107±25.4	114±36.8	153±51.3*†
(RV/TLC), %Predicted	97±19.7	102±25.1	131±31.0*†
Post max bronchodilation			
n	58	348	244
FEV_1 Max, %Predicted	106±12.1	94±14.5†	75±20.0*†
FVC Max, %Predicted	105±13.5	99±13.8†	88±17.3*†
(FEV_1/FVC) Max, %Predicted	101±7.2	95±10.0†	84±14.4*†

RV/TLC ratio is higher in patients with severe asthma compared to non-severe

Sorkness RL et al , J Appl Physiol. 2008; 104: 394403

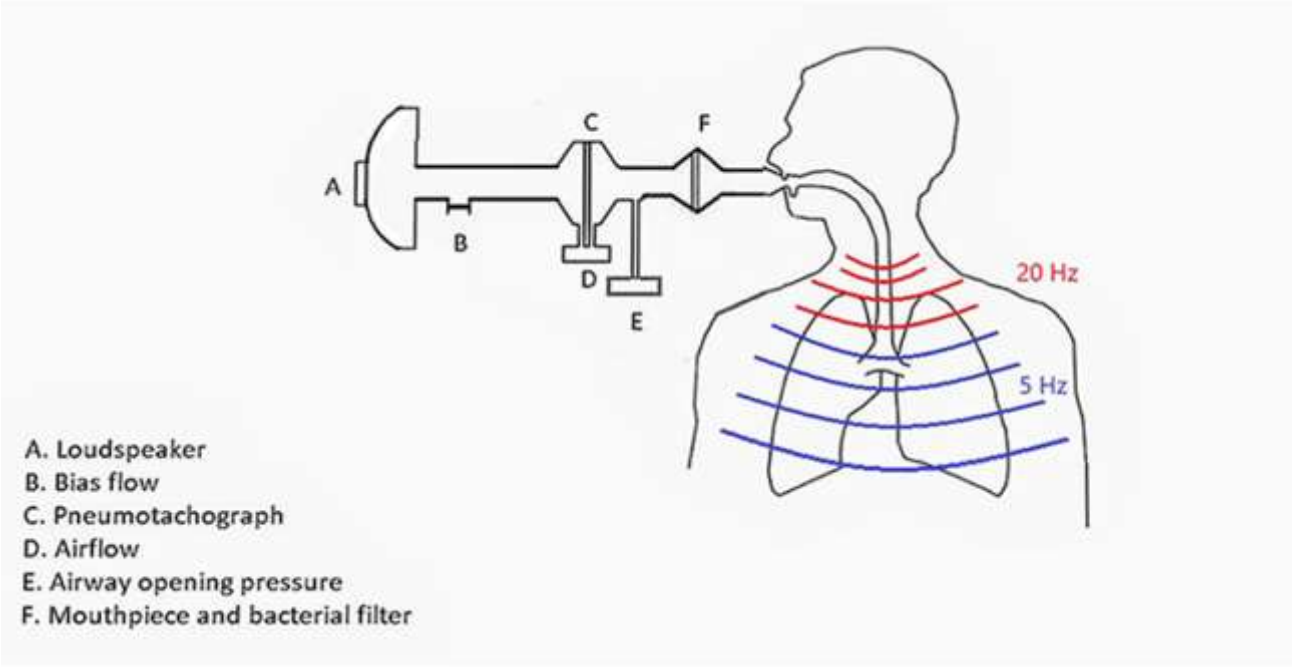
Body Plethysmography

- Not specific for small airways disease
- Effort dependent
- Relatively time consuming

- Marked obesity
- Skeletal abnormalities
- Claustrophobia

Oscillometry

- In 1956 Dubois et al. described the forced oscillation technique (FOT) to measure lung functions using single frequency sound waves
- In 1975, Michaelson et al. improvised the technique to use multiple frequency sound waves which was named impulse oscillometry (IOS)

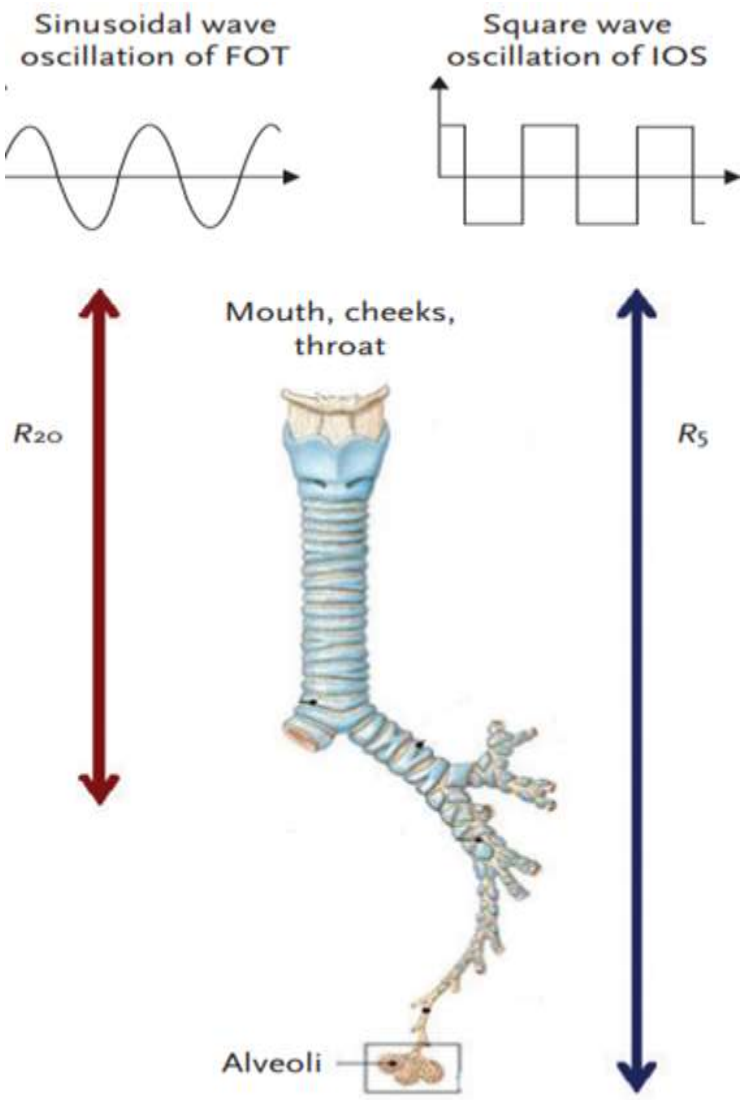


- **Higher frequencies (20 Hz)** travel shorter distances -large airway resistant (R20)
- **Lower frequencies (5 Hz)** travel larger distances -total airway resistance (R5)
- **(R5–R20)** - resistance in the small airways

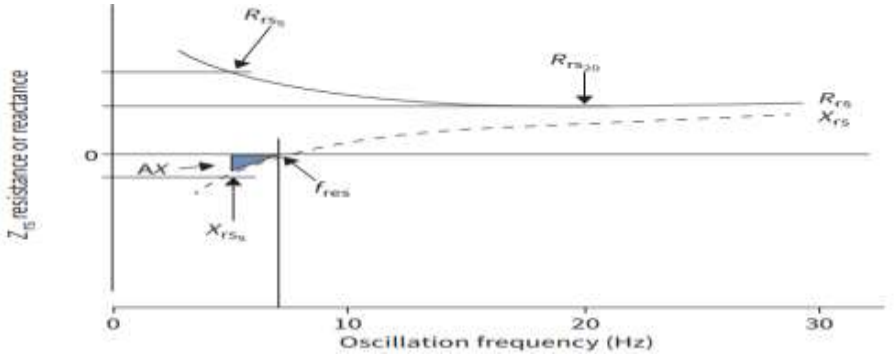
Adv Respir Med. 2019; 87: 235–238

FOT vs IOS

	FOT	IOS
Wave	sinusoidal sound waves	square wave oscillatory pressure
Frequencies	single frequencies	multiple frequencies
Resolution	good time resolution	temporal resolution of IOS is slightly inferior to FOT
Comfort	easy to perform	bit uncomfortable



Oscillometry

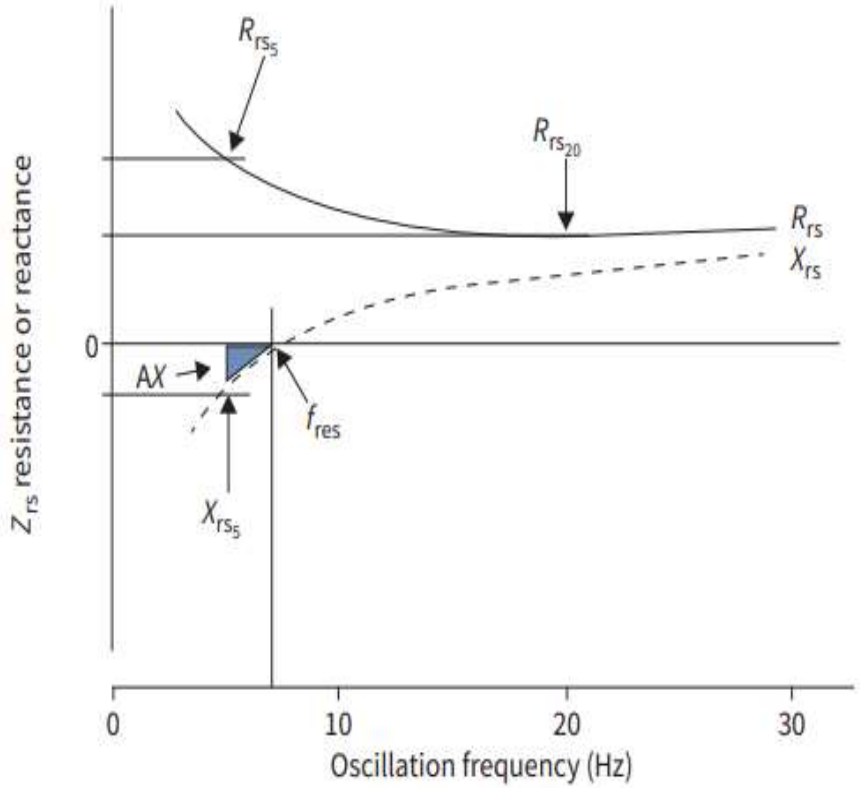


- **Respiratory resistance (Rrs)** is the in-phase component of lung impedance and reflects information about the forward pressure of the conducting airways
- **Respiratory reactance (Xrs)** is the out-of-phase component (imaginary part) of lung impedance and reflects the **capacitive(C)** and **inertive (I)** properties (opposite forces) of the airways
- **Respiratory impedance (Zrs)** is the sum of all forces which oppose the generated impulse, i.e. real respiratory resistance and imaginary respiratory reactance
- **Zrs(f)= Rrs(f)+ Xrs(f**)

Smith, Hj et al.European Respiratory Monograph 31 (2005): 72-105.

Oscillometry

- **Reactance at 5 Hz (X5**) reflects the elastic recoil of the peripheral airways (capacitive energy of the lungs)
- **Resonant frequency (Fres)** indicates the frequency at which the inertial properties of the airways and capacitance of lung periphery are equal. Total reactance at this point is zero
- **Area of reactance (AX-Goldman Triangle)** is the integrated low frequency respiratory reactance magnitude between 5 Hz and Fres
- IOS quality assurance is measured by **coherence (CO)**



Smith, Hj et al.European Respiratory Monograph 31 (2005): 72-105.

Parameter	Physiological interpretation
Zrs	Total forces related **to resistance, elastance and inertance** that must be overcome to drive airflow into and out of the lung. Zrs broadly describes the **mechanical properties of the entire respiratory system (airway, parenchyma and chest wall).**
Rrs	**Resistance of the respiratory system**, reflecting fractional losses both in gases as they flow along **airways and in tissues of the lung and chest wall** . Changes in Rrs at higher frequencies **above ~5 Hz** are reflective of changes **in airway resistance**, i.e. caliber, and thus sensitive to airway narrowing. **Tissue resistance** becomes progressively more important as frequency **decreases below 5 Hz**, becoming dominant
Xrs	Reflecting respiratory system **elastance (Ers)** due to the combined stiffnesses of **the lung and chest wall** tissues (below fres), and respiratory system **inertance (Irs**) due to the mass of gas in the **central airways** (above the fres). Xrs becomes “more negative”- respiratory system becomes stiffer
fres	**Ers** makes the major contribution to Xrs as frequency decreases below fres, while **Irs** dominates increasingly above fres
AX	**The area under the reactance curve (AX)** is the area inscribed by the Xrs curve between the lowest measured frequency and fres. **Determined predominately by Ers**. Assessing AX (considering Xrs at all frequencies below fres) in the clinic is potentially more sensitive to changes in the **elastic properties of the respiratory system** than Xrs at a single frequency

Eur Respir Rev 2022; 31: 210208

Oscillometry-interpretation

Diseases	Parameters
Proximal airway obstruction	Increased R5, increased R20, normal X5 and normal Fres.
Peripheral airway obstruction	Increased R5, normal R20, increased X5 and increased Fres
Lung restriction	Normal R5, normal R20, increased X5, increased Fres
Bronchodilator response	40% decrease in Rrs at 5 Hz, 50% increase in Xrs at 5 Hz and 80% decrease in AX relative to baseline
Bronchoconstrictor response	20 to 50% increase in Rrs5 and a 20–80% decrease in Xrs5 .

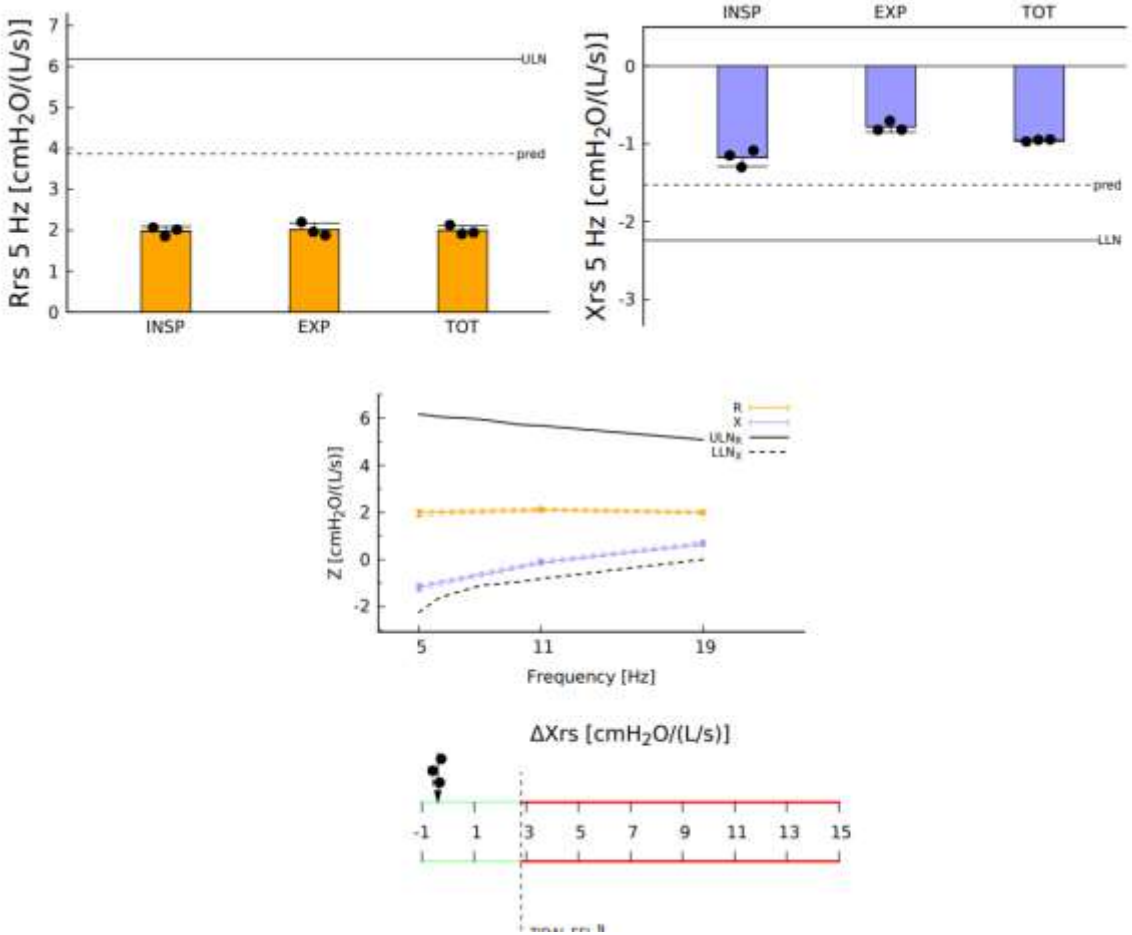
Eur Respir Rev 2022; 31: 210208

Oscillometry-interpretation

- Discrimination of inspiratory and expiratory resistance and reactance
- Expiratory reactance falls when EFL is present as the pressure signals cannot pass the choke point with in the airway-dynamic hyperinflation

Eur Respir Rev 2022; 31: 210208

FOT


Rrs 5 Hz [cmH2O/(L/s)]
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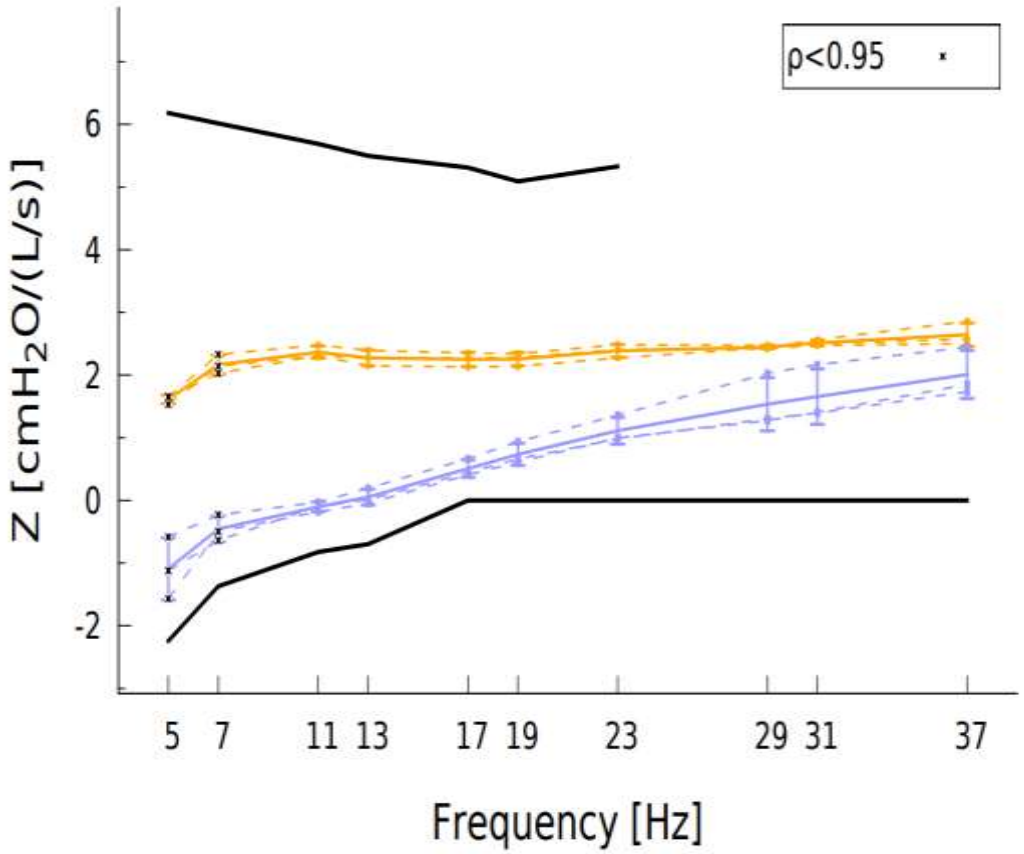
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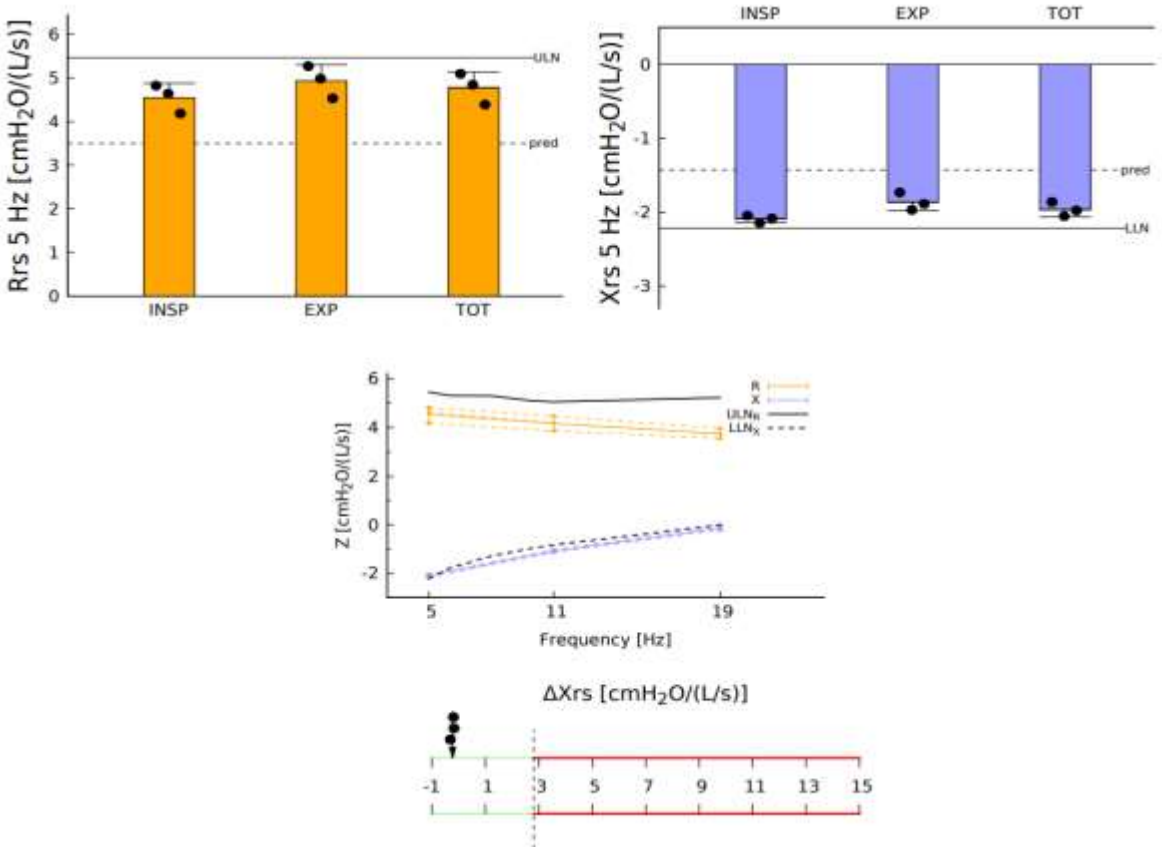


Height (cm) 161 4 Weight (Kg) 71 BSA (m^2) 1.75

Pre Bronchodilator	Observed	Predicted	LLN	% Predicted
FVC (L)	2.28	2.87	2.14	79
FEV_1 (L)	1.30	2.18	1.65	60
FEV_1/FVC %	57.0	84.6	75.1	—
PEFR (L/Min)	209.3	315.3	291.4	56
$FEF_{25-75\%}$ (L/Min)	34.8	166.7	90.2	21

Post Bronchodilator	Observed	% Improvement	Improvement (ML)
FVC (L)	2.41	5.7 %	130 ml
FEV_1 (L)	1.47	13.0 %	170 ml
FEV_1/FVC %	61.0		
PEFR (L/Min)	236.6		
$FEF_{25-75\%}$ (L/Min)	49.2		

Original Article

Small Airway Dysfunction by Impulse Oscillometry in Symptomatic Patients with Preserved Pulmonary Function

BACKGROUND: Asthma and chronic obstructive pulmonary disease are characterized by persistent airway inflammation and airflow limitation. Early detection of these diseases in patients with respiratory symptoms and preserved pulmonary function (PPF) defined by spirometry is difficult. Impulse oscillometry (IOS) may have better sensitivity than effort-dependent forced expiratory flow between 25% and 75% ($FEF_{25\%-75\%}$) to detect small airway dysfunction (SAD).

OBJECTIVE: To identify SAD in patients with respiratory symptoms and PPF using IOS.

METHODS: Medical records of symptomatic patients without acute or known structural lung diseases were evaluated. Patients had bronchodilator testing and IOS in the outpatient clinic between March 1 and July 31, 2017. Correlations between respiratory symptoms, spirometry, and IOS parameters were determined.

RESULTS: Among 349 patients enrolled to the study, 255 (73.1%) patients met the criteria of PPF. The IOS parameters—difference in resistance at 5 Hz and resistance at 20 Hz , reactance at 5 Hz, resonant frequency (F_{res}), and area under reactance curve between 5 Hz and resonant frequency—were significantly correlated with $FEF_{25\%-75\%}$. The cutoffs for SAD were difference in resistance at 5 Hz and resistance at 20 Hz greater than 0.07 kPa/(L/s), reactance at 5 Hz less than −0.12 kPa/(L/s), F_{res} greater than 14.14 Hz, and area under reactance curve between 5 Hz and resonant frequency greater than 0.44 kPa/L. Of the IOS parameters, F_{res} and reactance at 5 Hz had the highest sensitivity and specificity. When compared with $FEF_{25\%-75\%}$, F_{res} had greater sensitivity to detect SAD in patients with PPF. Patients with IOS-defined SAD had a significantly higher incidence of wheeze or sputum production than did those defined by $FEF_{25\%-75\%}$.

CONCLUSIONS: Patients with respiratory symptoms and PPF may have SAD, which can be identified with the aid of IOS in addition to spirometry.

Chiu HY, et al. J Allergy Clin Immunol Pract. 2020 Jan;8(1):229-235.e3.

Small Airway Dysfunction by Impulse Oscillometry in Symptomatic Patients with Preserved Pulmonary Function

TABLE III. Cutoff values of SAD-related IOS parameters in patients with PPF (N = 255)

IOS parameter	Cutoff value	Sensitivity (%)	Specificity (%)	LR (+)	LR (−)	AUC	Youden index	*P* value
$R_5 - R_{20}$	>0.07	62.5	59.7	1.55	0.63	0.62	0.22	<.01
X_5	<−0.12	46.9	77.5	2.08	0.69	0.64	0.24	<.01
F_{res}	>14.14	75.0	57.9	1.78	0.43	0.69	0.33	<.01
AX	>0.44	65.6	61.9	1.72	0.56	0.67	0.28	<.01

TABLE V. Incidence of SAD defined by $FEF_{25\%-75\%}$ and IOS parameters

	Nonobstructive group ($FEV_1/FVC \geq 0.7$)		Obstructive group ($FEV_1/FVC < 0.7$)	
Small airway parameter	BR (−) (N = 255)	BR (+) (N = 16)	BR (−) (N = 62)	BR (+) (N = 16)
$FEF_{25\%-75\%}$ <65% predictted, n (%)	64 (25.1)	10 (62.5)	62 (100)	16 (100)
$R_5 - R_{20} > 0.07$, n (%)	127 (49.8)	7 (43.8)	50 (80.6)	14 (87.5)
$X_5 < -0.12$, n (%)	74 (29.0)	7 (43.8)	39 (62.9)	14 (87.5)
$F_{res} > 14.14$ Hz, n (%)	128 (50.2)	11 (68.8)	54 (87.1)	15 (93.8)
AX > 0.44, n (%)	111 (43.5)	10 (62.5)	51 (82.3)	15 (93.8)

Chiu HY et al., J Allergy Clin Immunol Pract. 2020 Jan;8(1):229-235.e3.

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

Abstract

Background: Subjects with chronic respiratory symptoms and preserved pulmonary function (PPF) may have small airway dysfunction (SAD). As the most common means to detect SAD, spirometry needs good cooperation and its reliability is controversial. Impulse oscillometry (IOS) may complete the deficiency of spirometry and have higher sensitivity. We aimed to explore the diagnostic value of IOS to detect SAD in symptomatic subjects with PPF.

Methods: The evaluation of symptoms, spirometry and IOS results in 209 subjects with chronic respiratory symptoms and PPF were assessed. ROC curves of IOS to detect SAD were analyzed.

Results: 209 subjects with chronic respiratory symptoms and PPF were included. Subjects who reported sputum had higher R5–R20 and Fres than those who didn't. Subjects with dyspnea had higher R5, R5–R20 and AX than those without. CAT and mMRC scores correlated better with IOS parameters than with spirometry. R5, R5–R20, AX and Fres in subjects with SAD (n = 42) significantly increased compared to those without. Cutoff values for IOS parameters to detect SAD were 0.30 kPa/L s for R5, 0.015 kPa/L s for R5–R20, 0.30 kPa/L for AX and 11.23 Hz for Fres. Fres has the largest AUC (0.665, P = 0.001) among these parameters. Compared with spirometry, prevalence of SAD was higher when measured with IOS. R5 could detect the most SAD subjects with a prevalence of 60.77% and a sensitivity of 81% (AUC = 0.659, P = 0.002).

Conclusion: IOS is more sensitive to detect SAD than spirometry in subjects with chronic respiratory symptoms and PPF, and it correlates better with symptoms. IOS could be an additional method for SAD detection in the early stage of diseases.

Li et al. Respir Res (2021) 22:68

Detection of expiratory flow limitation in COPD using the forced oscillation technique

R.L. Dellacà*, P. Santus#, A. Aliverti*, N. Stevenson¶, S. Centanni#, P.T. Macklem+, A. Pedotti*, P.M.A. Calverley¶

Detection of expiratory flow limitation in COPD using the forced oscillation technique. R.L. Dellacà, P. Santus, A. Aliverti, N. Stevenson, S. Centanni, P.T. Macklem, A. Pedotti, P.M.A. Calverley. ©ERS Journals Ltd 2004.

ABSTRACT: Expiratory flow limitation (EFL) during tidal breathing is a major determinant of dynamic hyperinflation and exercise limitation in chronic obstructive pulmonary disease (COPD). Current methods of detecting this are either invasive or unsuited to following changes breath-by-breath. It was hypothesised that tidal flow limitation would substantially reduce the total respiratory system reactance (X_{rs}) during expiration, and that this reduction could be used to reliably detect if EFL was present.

To test this, 5-Hz forced oscillations were applied at the mouth in seven healthy subjects and 15 COPD patients (mean±SD forced expiratory volume in one second was 36.8±11.5 % predicted) during quiet breathing. COPD breaths were analysed (n=206) and classified as flow-limited if flow decreased as alveolar pressure increased, indeterminate if flow decreased at constant alveolar pressure, or nonflow-limited.

Of these, 85 breaths were flow-limited, 80 were not and 41 were indeterminate. Among other indices, mean inspiratory minus mean expiratory X_{rs} ($\Delta\overline{X_{rs}}$) and minimum expiratory X_{rs} ($X_{exp,min}$) identified flow-limited breaths with 100% specificity and sensitivity using a threshold between 2.53–3.12 $cmH_2O \cdot s \cdot L^{-1}$ ($\Delta\overline{X_{rs}}$) and -7.38– -6.76 $cmH_2O \cdot s \cdot L^{-1}$ ($X_{exp,min}$) representing 6.0% and 3.9% of the total range of values respectively. No flow-limited breaths were seen in the normal subjects by either method.

Within-breath respiratory system reactance provides an accurate, reliable and noninvasive technique to detect expiratory flow limitation in patients with chronic obstructive pulmonary disease.

Eur Respir J 2004; 23: 232–240.

Expiratory reactance falls when EFL is present as the pressure signals cannot pass the choke point with in the airway--dynamic hyperinflation

Dellaca et al.,Eur Respir J 2004; 23: 232–240.

Oscillometry

- Effort-independent
- Requires minimal patient cooperation
- Can be performed in tidal breathing
- Distinguish between the degree of obstruction in central and peripheral airways
- Equipment not widely available
- Interference from swallowing and upper airway artefact

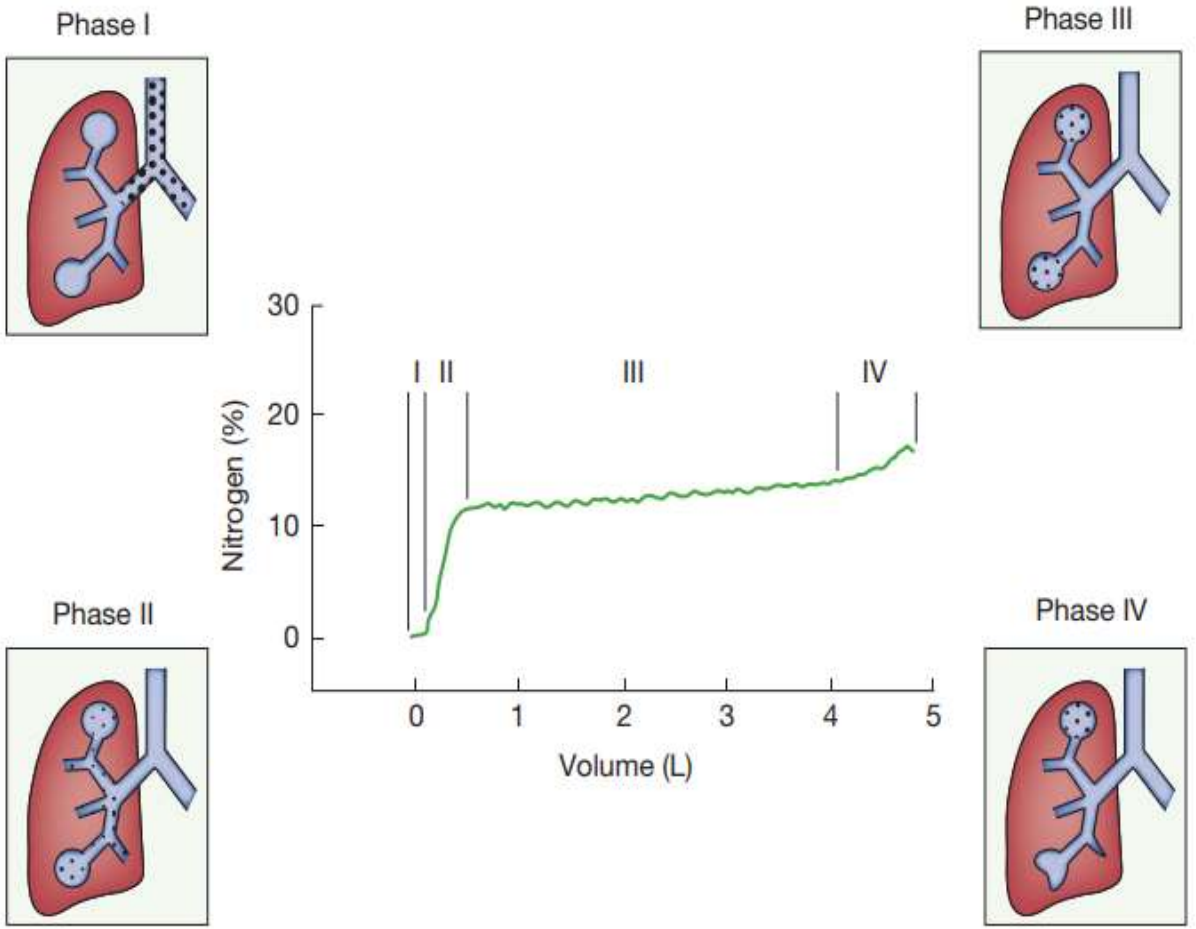
Inert gas washout

- Single breath nitrogen washout (SBNW)
- Multiple breath nitrogen washout (MBNW)
- Helium and Sulphur hexafluoride washout tests

Single-Breath Nitrogen Washout

- Seated patient takes two deep breaths of air and then expires to RV.
- Maximal expiration, a valve is opened so that the patient can take a full breath of 100% O_2 to TLC
- The patient then expires slowly to RV while N2 concentration and expired volume are recorded continuously

Single-Breath Nitrogen Washout



Four distinct phases identified in the continuous record relating N2 concentration to expired volume

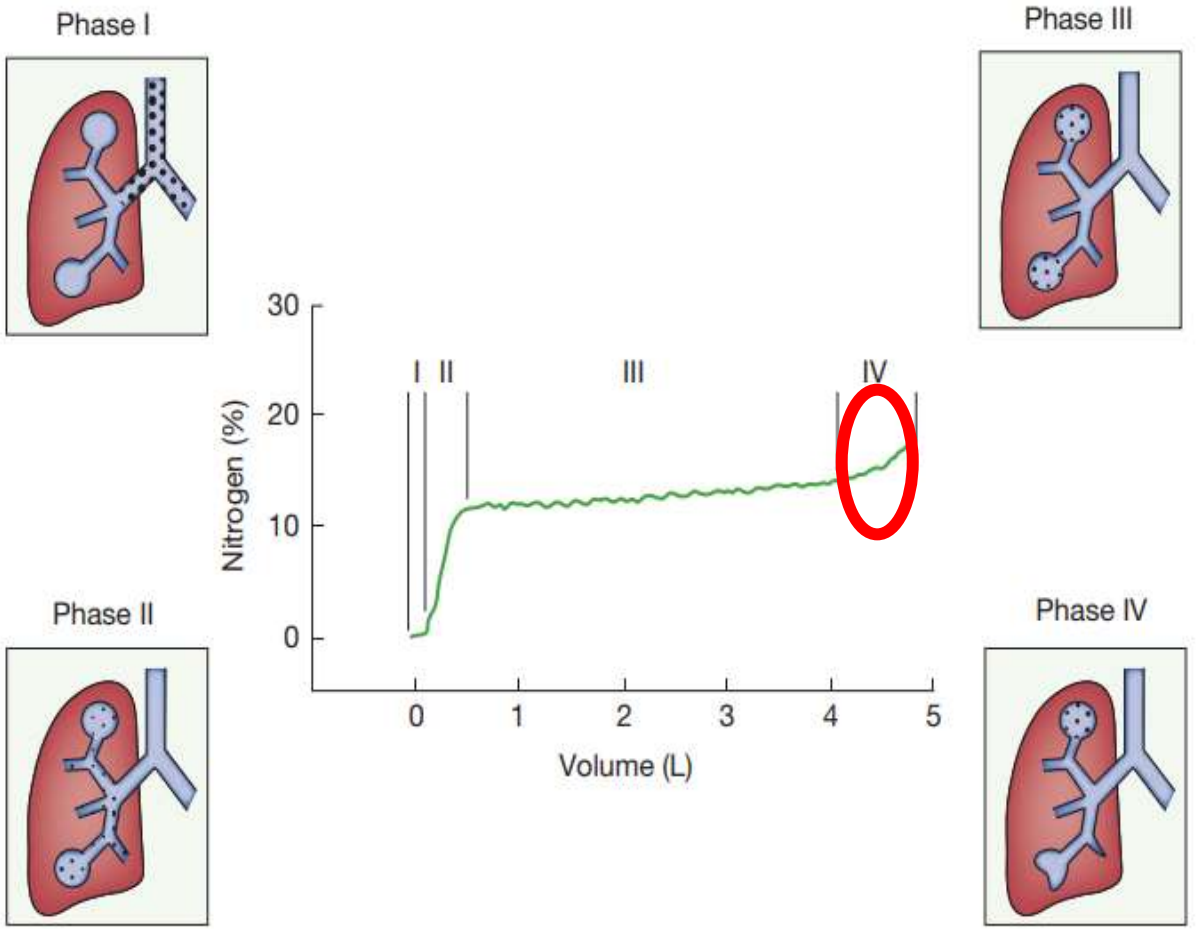
Phase I-containing dead space.

Phase II -represents a mixture of gases from the dead space and the alveoli.

Phase III- due to a mixture of gases from alveoli located at the apices, midlung fields, and bases.

Phase IV- characterized by an upward shift in N2 concentration, is caused by closure of alveoli in the dependent parts of the lungs at low lung volumes.

Single-Breath Nitrogen Washout



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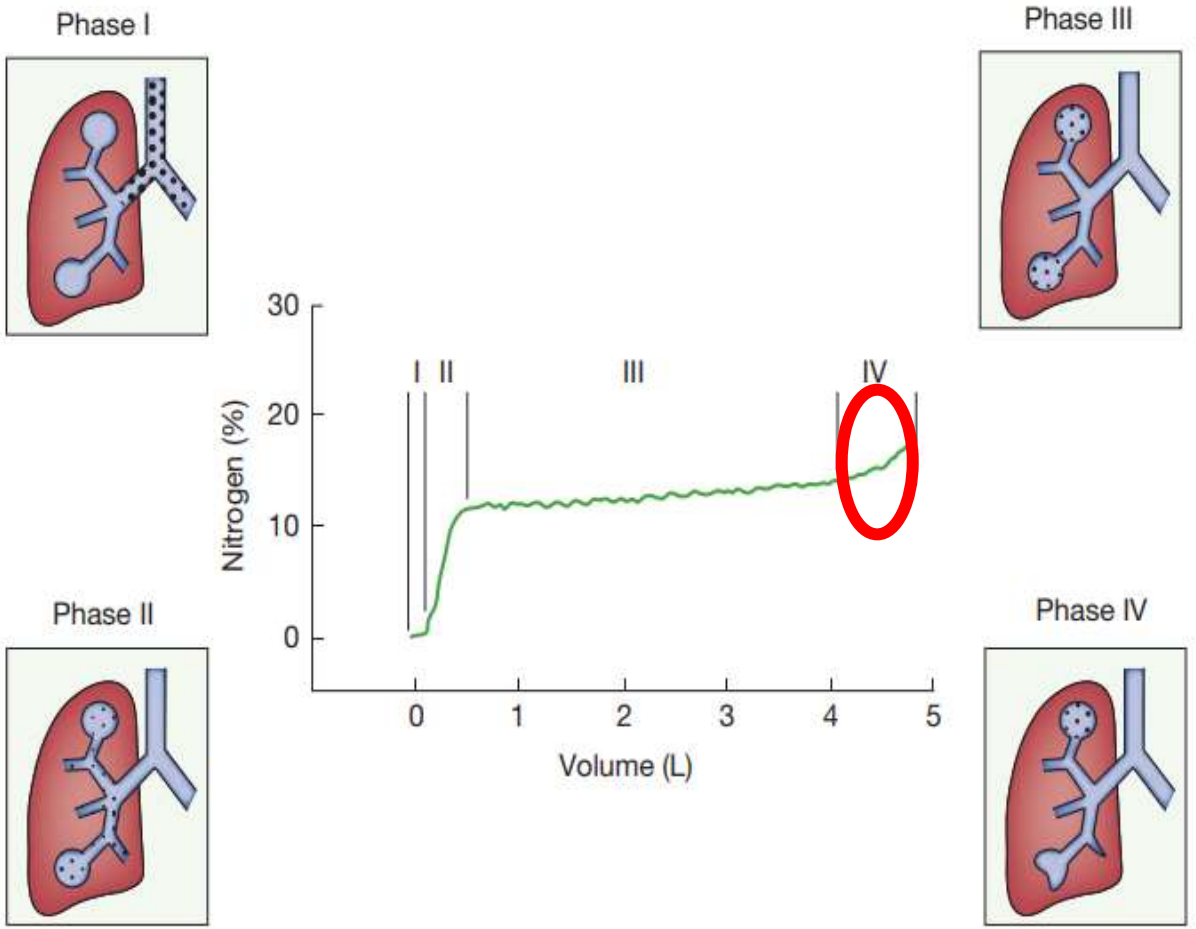
Single-Breath Nitrogen Washout

- Closing volume (CV)-volume from the onset of phase IV to the completion of the full expiratory maneuver
- CV +RV = closing capacity (CC)
- Narrowing or obstruction of small peripheral airways causes closing volume to enlarge
- Healthy young adults, the normal closing volume averages about 10% of the VC
- Closing volume also increases progressively as people grow older,that by the age of 50, the closing volume sometimes reaches 25% of the VC.

Single-Breath Nitrogen Washout



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Single-Breath Nitrogen Washout

- Analysis of the slope of phase III (SIII) provides information on the **ventilation heterogeneity**
- Conducting airways -gas flows by convection (convection-dependent ventilation inhomogeneity, **CDI**) and results from narrowing of airways or increased stiffness in the subtended lung units.
- In distal acinar airways -the diffusion convection (diffusion convection-dependent inhomogeneity**, DCDI**)
- Airways disease- affected lung units **mix less well with the inspired oxygen** (and thus have a higher nitrogen concentration) and empty more slowly. This causes an increase in SIII

McNulty W et al.. Eur Clin Respir J. 2014 Oct 17;1

Single-Breath Nitrogen Washout

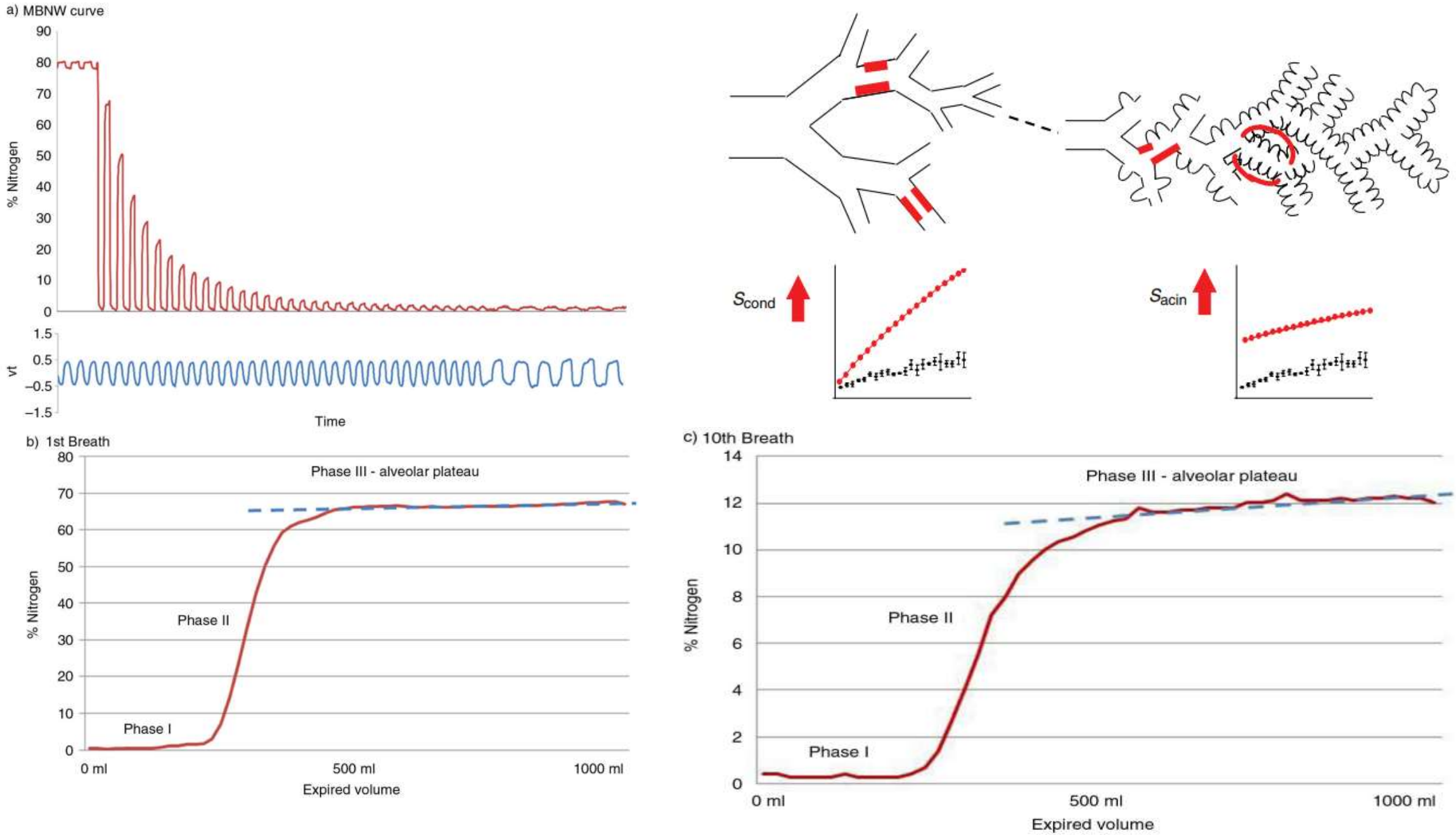
- SBNW is sensitive to early changes in airways in smokers with an increase in CV
- CC/TLC ratio predicted the rate of decline in FEV1 suggesting it may be useful in identifying at risk smokers
- SBNW is not specific to small airways pathology
- Changes in any of the generations of the conducting airways will also affect the slope of phase III

McNulty W et al.. Eur Clin Respir J. 2014 Oct 17;1

Multiple breath nitrogen washout

- MBNW is a modification of the single breath technique
- The patient inhales 100% O2 from FRC with a fixed TV and respiratory rate to wash out the resident nitrogen from the lungs.
- The test continues until the exhaled nitrogen is less than **1/40th** of the original concentration (approximately **2%**) for three successive breaths
- Speed and efficiency of gas mixing is determined by tidal volume, breath frequency, and ventilation heterogeneity.
- Thus, by keeping breath frequency and tidal volume relatively **constant**, inferences about ventilation heterogeneity can be made

Verbanck S, Paiva M. Gas mixing in the airways and airspaces. Compr Physiol. 2011 Apr;1(2):809-34.


a) MBNW curve
% Nitrogen
90
80
70
60
50
40
30
20
10
0
vt
1.5
0.5
−0.5
−1.5
Time
b) 1st Breath
Phase III - alveolar plateau
Phase II
Phase I
% Nitrogen
80
70
60
50
40
30
20
10
0
0 ml
500 ml
1000 ml
Expired volume
S_{cond}
S_{acin}
c) 10th Breath
Phase III - alveolar plateau
Phase II
Phase I
% Nitrogen
14
12
10
8
6
4
2
0
0 ml
500 ml
1000 ml
Expired volume

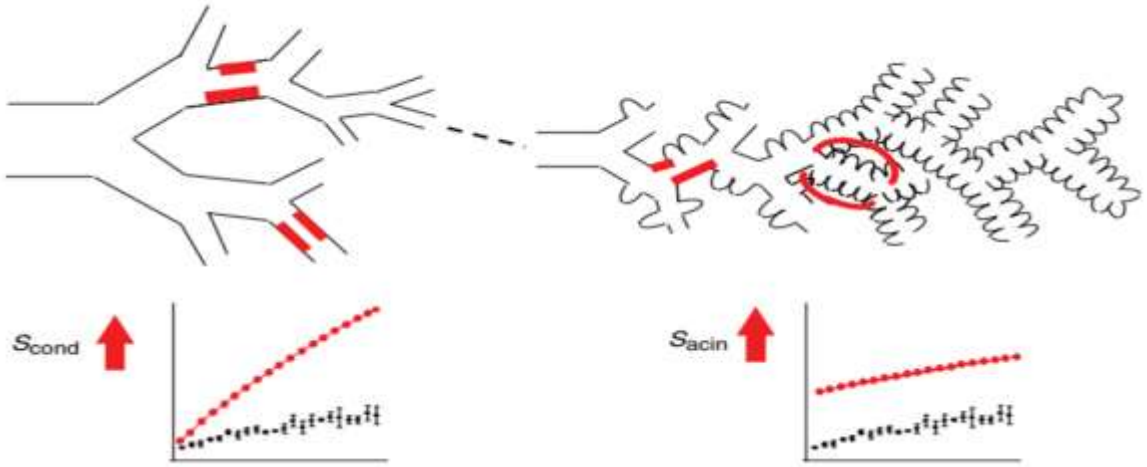
Multiple breath nitrogen washout

- Efficiency of gas mixing in the whole lung -**the lung clearance index (LCI**)
- LCI-defined as the number of lung turnovers (FRC equivalents) required to wash out the tracer gas to 1/40th of the original concentration
- Cumulative expired volume (CEV) required to washout the resident nitrogen divided by FRC = LCI
- As a MBNW progresses, the SIII of each breath changes throughout the test, becoming steeper with successive breaths

Verbanck S, Paiva M. Gas mixing in the airways and airspaces. Compr Physiol. 2011 Apr;1(2):809-34.

Multiple breath nitrogen washout

- In normal lungs, the DCDI is the major determinant of the SNIII and reaches its maximum at approximately 1.5 lung turnovers. After this, the increase in SNIII is diffusion independent and hence reflects CDI
- Distinguish **ventilation heterogeneity** arising within proximal conducting airways (**Scond**) from that arising in more distal airways within the region of the lung acinus (**Sacin**)



Verbanck S, Paiva M. Gas mixing in the airways and airspaces. Compr Physiol. 2011 Apr;1(2):809-34.

Inert Gas Washout in Bronchiolitis Obliterans Following Hematopoietic Cell Transplantation

Sylvia Nyilas; Luzia Baumeler; Michael Tamm; Jörg P. Halter; Spasenija Savic; Insa Korten; Anja Meyer; Florian Singer; Jakob R. Passweg; Philipp Latzin; and Daiana Stolz

BACKGROUND: Bronchiolitis obliterans syndrome (BOS) is a leading cause of chronic graft-vs-host disease (cGvHD) and is associated with mortality after allogeneic hematopoietic stem cell transplantation (alloHSCT). The nitrogen multiple breath washout test (N_2-MBW) measures ventilation inhomogeneity, a biomarker of central and peripheral airway obstruction. The aim of this study was to examine ventilation inhomogeneity according to cGvHD score and histologically defined bronchiolitis obliterans (BO).

METHODS: This single-center prospective cross-sectional study included 225 adults (mean age, 52.8 years; median, 5.4 years (interquartile range, 2.0-11 years) after alloHSCT). Outcomes were global (lung clearance index [LCI]) and acinar ventilation inhomogeneity index (S_{ACIN}) from N_2-MBW. Patients were categorized into five groups: (1) no cGvHD and no obstruction (cGvHD overall score 0 and $FEV_1/FVC \geq 70$) (2) cGvHD and no obstruction (cGvHD overall score 1-3 and $FEV_1/FVC \geq 70$), (3) BOS with or without cGvHD (if available, no BO on histologic examination, and $FEV_1/FVC < 70$), (4) histologically proven BO, and (5) diffuse parenchymal lung disease other than BO.

RESULTS: The LCI and S_{ACIN} differed significantly between groups ($P < .001$) and increased progressively according to cGvHD score. In BO, the LCI and S_{ACIN} were elevated in 95.5% and 81.8% of patients, respectively, whereas FEV_1/FVC was abnormal in only 56.5% of patients, respectively.

CONCLUSIONS: N_2-MBW is highly sensitive for detecting abnormal lung function in patients following alloHSCT. LCI and S_{ACIN} seem to be promising biomarkers of lung involvement in cGvHD.

CHEST 2017; ■(■):■-■

Nyilas S,et al., Chest. 2018 Jul;154(1):157-168

Multiple breath nitrogen washout

- Sensitive to early change
- Can distinguish between distal and proximal airways disease
- Not specific to small airways
- Research settings
- Few commercially available machines
- Interpretation of results can be difficult

Helium and Sulphur hexafluoride washout tests

- Inert tracer gas must be safe to inhale and not participate in gas exchange.
- Exogenous gases (sulfur hexafluoride (SF6) and helium) must be washed-in before they are washed out by breathing room air, whereas endogenous gases (nitrogen) are washed-out by breathing 100% oxygen
- The diffusion front of helium lies more proximally than SF6 and therefore changes in the helium SIII compared to SF6 SIII suggest more proximal acinar changes
- Difficult to perform, requiring specialist equipment, restricted to research settings

McNulty W et al.. Eur Clin Respir J. 2014 Oct 17;1

CYSTIC FIBROSIS

Multiple breath inert gas washout as a measure of ventilation distribution in children with cystic fibrosis

P Aurora, P Gustafsson, A Bush, A Lindblad, C Oliver, C E Wallis, J Stocks

Thorax 2004;**59**:1068–1073. doi: 10.1136/thx.2004.022590

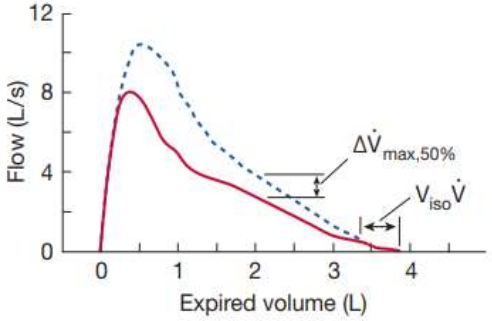
See end of article for authors' affiliations

Correspondence to: Dr P Aurora, Portex Anaesthesia, Intensive Therapy and Respiratory Medicine Unit, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK; p.aurora@ich.ucl.ac.uk

Background: Multiple breath inert gas washout (MBW) has been suggested as a tool for detecting early cystic fibrosis (CF) lung disease. A study was undertaken to compare the relative sensitivity of MBW and spirometry for detecting abnormal lung function in school age children with CF and to compare MBW results obtained from healthy children in the UK with those recently reported from Sweden.
Methods: Forced expiratory volume in 1 second (FEV_1) and maximal expiratory flow when 25% of forced vital capacity remains to be expired (MEF_{25}) were compared with the lung clearance index (LCI) derived from sulphur hexafluoride MBW in 22 children with CF aged 6–16 years and in 33 healthy controls.
Results: LCI was higher in children with CF than in healthy controls (mean difference 5.1 (95% CI of difference 4.1 to 6.1) and FEV_1 and MEF_{25} z-scores were lower (mean difference −2.3 (95% CI −2.9 to −1.7) and −1.8 (95% CI −2.4 to −1.3), respectively; $p<0.001$ for all). There was a significant negative correlation between LCI and FEV_1 ($r^2=0.62$) and MEF_{25} ($r^2=0.46$). However, while normal (≥ -1.96 z-scores) FEV_1 and MEF_{25} results were seen in 11 (50%) and 12 (53%) children with CF, respectively, all but one of these children had an abnormally increased LCI. LCI was repeatable in both groups (within subject CV for three measurements 6% for CF and 5% for healthy children). In healthy subjects LCI was independent of age and virtually identical in the British and Swedish children (mean difference 0.1 (95% CI −0.1 to 0.4), p=0.38)

Thorax 2004;59:1068–1073

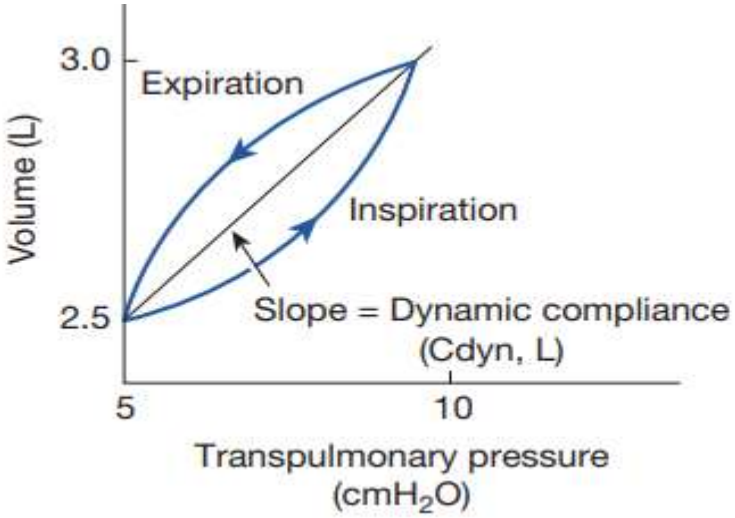
Helium-Oxygen Flow-Volume Curves

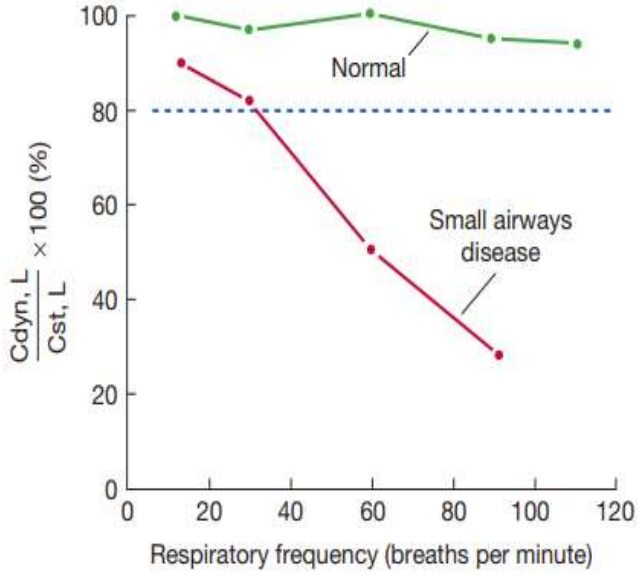


- Normal subjects, at **lung volumes greater than 10% of the VC**, the primary site of resistance to airflow is in the **larger airways, turbulent flow and density dependent**
- At these lung volumes, the flow attained with the helium-oxygen mixture will be higher than that attained with air
- At lung **volumes less than 10% of the VC**, the primary site of resistance is in the **smaller airways, laminar flow and not density dependent**. The less dense helium mixture has no effect on flow
- In disease of the small airways, the primary site of resistance shifts at large volumes from the larger to the smaller airways
- The flow-enhancing effect of the less dense gas disappears at volumes well above 10% of the VC
- Volume of isoflow is normally less than 10% of the VC; when it is increased, it indicates small airway obstruction

Dynamic Compliance

- Dynamic compliance-$\partial V / dTp$ during airflow is normally independent of breathing frequency
- Under conditions of nonuniformity of ventilation throughout the lung, increases in breathing frequency are associated with a fall in dynamic compliance.
- In normal subjects, Cdyn,L/Cst,L remains above 0.8
- Presence of obstructive disease of the small airways, Cdyn,L/ Cst,L falls progressively to values below 0.8 as breathing frequency increases
- Respiratory frequency increases is the presence of unequal time constants throughout the lung





Woolcock AJ et al., J Clin Invest. 1969 Jun;48(6):1097-106

Exhaled nitric oxide

- Fractional exhaled nitric oxide (FENO) -measured in a single exhalation during tidal breathing
- Exhaled nitric oxide (eNO) exhibits flow rate dependency, with an inverse correlation between flow rate and FENO
- Under low flow conditions-reflects central airways
- At higher flows -alveolar NO
- Back-diffusion of NO between the alveolar and airway compartments complicates the interpretation of results.
- NO will diffuse from the airways down a concentration gradient into the alveoli, thus elevating alveolar NO and reducing measured airway NO

McNulty W et al.. Eur Clin Respir J. 2014 Oct 17;1

Alveolar nitric oxide in adults with asthma: evidence of distal lung inflammation in refractory asthma

ABSTRACT: Recent studies have suggested that alveolar nitric oxide (NO) concentration is a noninvasive test of distal lung inflammation.

The current study determined whether alveolar NO concentration can be measured in patients with asthma of varying severity, tested the hypothesis that there is an association between alveolar NO and bronchoalveolar lavage (BAL) eosinophil count and determined whether refractory asthma is characterised by a raised alveolar NO concentration. Finally, the present authors assessed the effect of 2 weeks of prednisolone (30 mg *q.d.*) on alveolar NO concentration.

Alveolar NO concentration was both measurable and repeatable in patients with refractory asthma. A positive correlation was found between alveolar NO concentration and BAL eosinophil count but not with bronchial wash or sputum eosinophil count. Alveolar NO concentration was increased in patients with refractory asthma (7.1 ppb) compared with mild-to-moderate asthma (3.4 ppb) and normal controls (3.4 ppb) and reduced by treatment with prednisolone.

In conclusion, these findings support the hypothesis that alveolar nitric oxide is a measure of distal airway inflammation and suggest that distal lung inflammation is present in refractory asthma.

M. Berry et al. Eur Respir J 2005; 25: 986–991

Alveolar nitric oxide versus measures of peripheral airway dysfunction in severe asthma

ABSTRACT: Alveolar nitric oxide (NO) is a measure of peripheral airway inflammation in asthma, potentially associated with disease severity. The relationship between alveolar NO and physiological tests of peripheral airway (dys)function has not been investigated. The present authors hypothesised that peripheral airway inflammation and dysfunction are inter-related and associated with asthma severity.

Alveolar NO was compared between 17 patients with mild-to-moderate asthma and 14 patients with severe asthma and related to total lung capacity (TLC), residual volume (RV)/TLC, thoracic gas volume (FRC), slope of the single breath nitrogen washout curve (dN_2), closing capacity (CC)/TLC and fall in forced vital capacity at the provocative concentration of methacholine causing a 20% fall in forced expiratory volume in one second. In patients with severe asthma, strong correlations were found between alveolar NO and RV/TLC % pred, FRC % pred, dN_2, and CC/TLC. Patients with oral steroid-dependent asthma had higher alveolar NO levels (2.7 ppb) compared with the other patients with severe (0.6 ppb) and mild-to-moderate asthma (0.3 ppb).

The present authors conclude that alveolar nitric oxide is closely related to parameters of peripheral airway dysfunction in patients with severe asthma, and that oral steroid-dependent asthmatics have more peripheral airway disease than nonsteroid-dependent asthmatics. This suggests that patients on chronic oral steroid treatment have more extensive disease and require additional anti-inflammatory treatment to better target the peripheral airways.

I.H. Van veen et al. Eur Respir J 2006; 27: 951–956

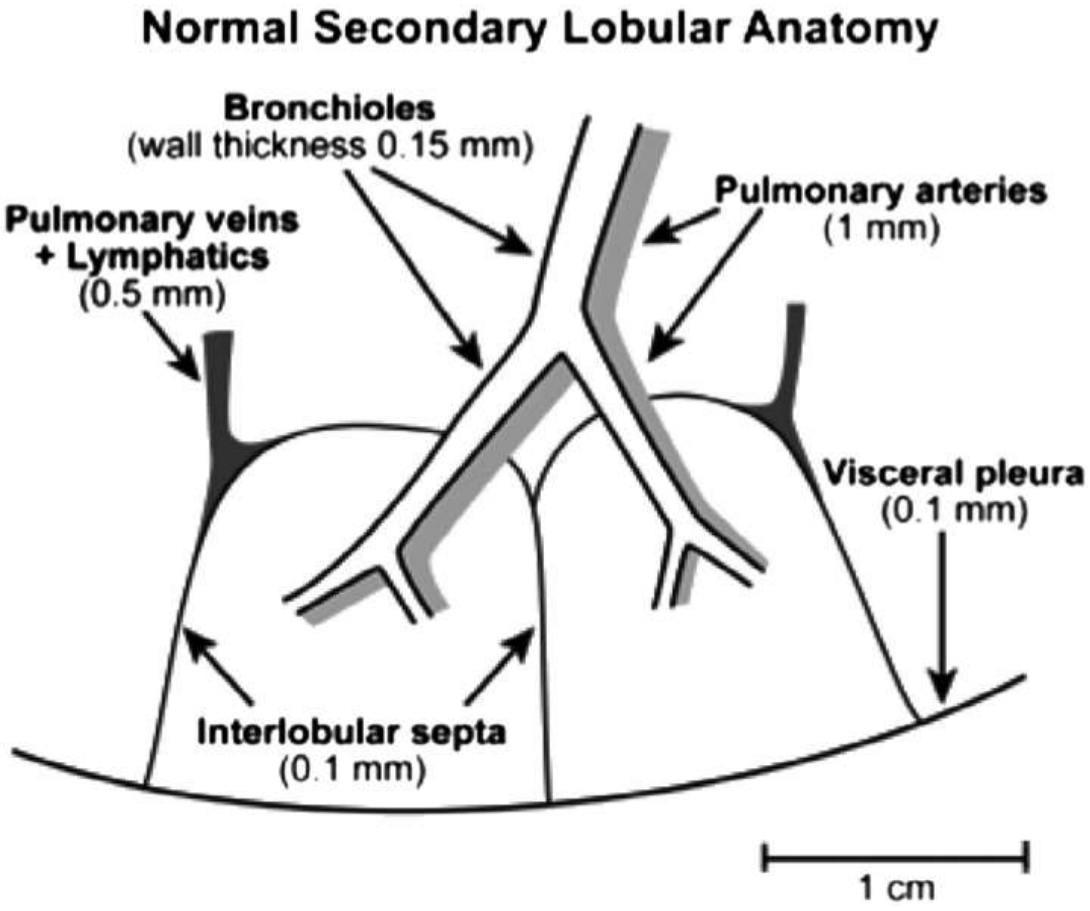
Exhaled nitric oxide -FE_{NO}

- Easy and quick to perform
- Hand-held analyzers available
- Sensitive to changes with treatment in asthma
- Unclear role in COPD
- Affected by smoking status
- Not much studied in small airway diseases

Imaging

Secondary pulmonary lobule

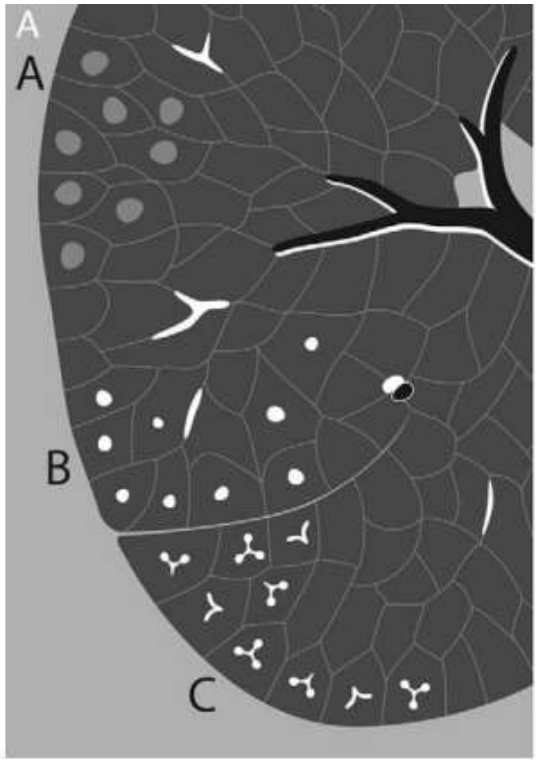
- Normal bronchioles are outside resolution of HRCT chest



Signs of small airways disease-HRCT

Direct Signs

- Centrilobular GGO
- Centrilobular nodules
- Branching and Tree in bud opacity
- Bronchial wall thickening
- Bronchiolectasis



Indirect Signs

Air Trapping
Mosaic Attenuation

Abbott et al .,J Thorac Imaging 2009;24:285–298

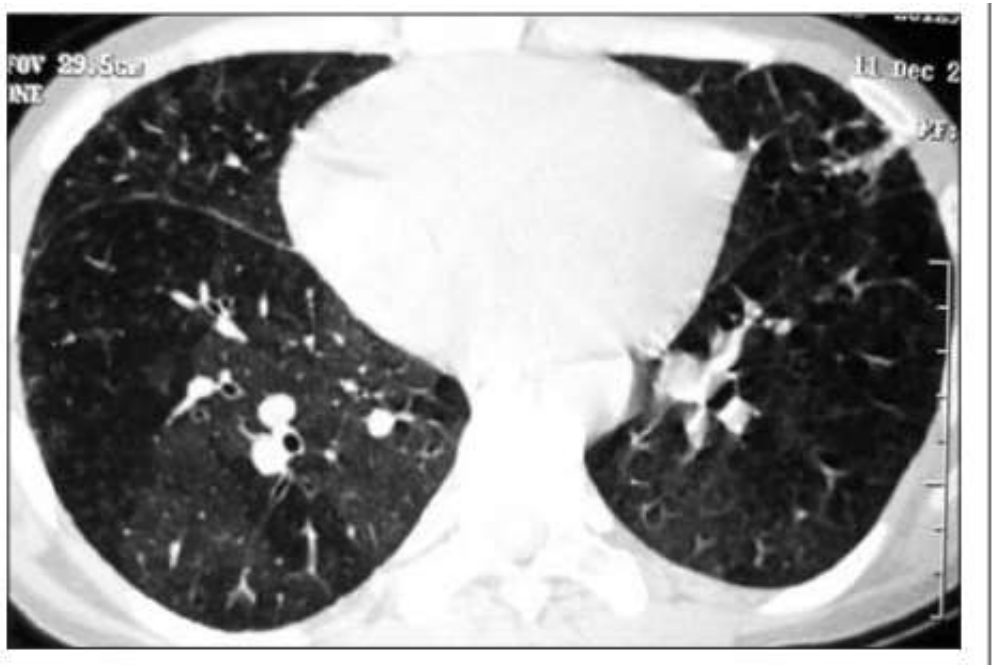
HRCT chest

- **Inspiratory and expiratory HRCT-** obtained using thin collimation (1.25 mm or less) acquired as either noncontiguous images at 1 cm or 2 cm intervals, or reconstructed from a spiral/ helical volumetric acquisition.
- **Minimum-intensity projection (MinIP) techniques** - detection of subtle areas of low attenuation, regional heterogeneity (mosaic attenuation) of lung parenchyma
- **Maximum-intensity projection (MIP) -** the recognition of small centrilobular nodules, tree-in-bud opacities, and poorly defined centrilobular nodules

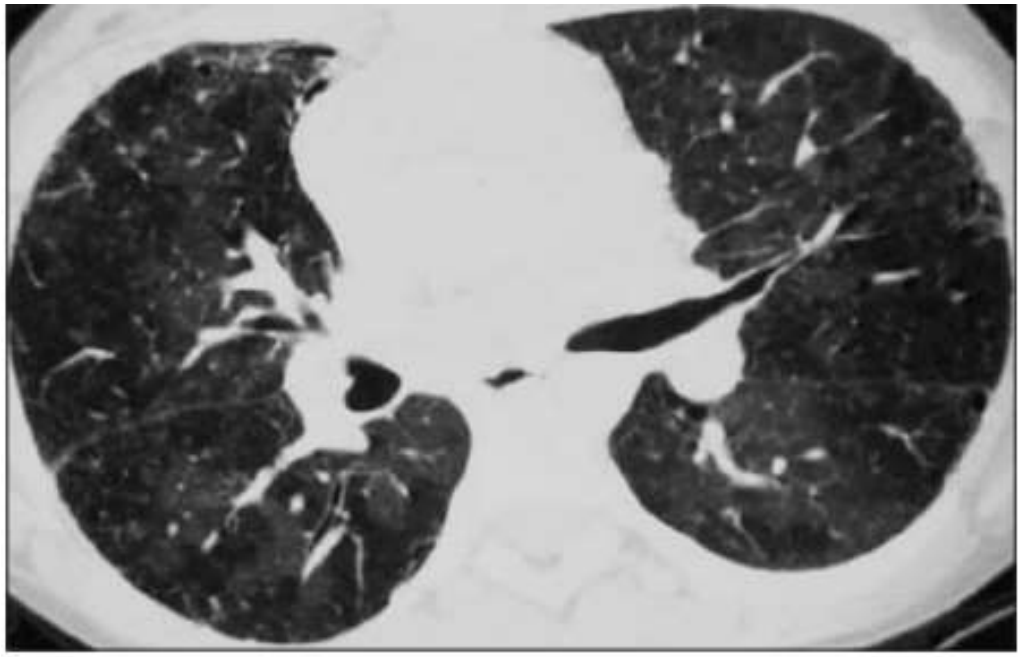
Abbott ,et al .J Thorac Imaging 2009;24:285–298

HRCT CHEST -TUBERCULAR BRONCHIOLITIS OBLITERANS

Mosaic attenuation



Air trapping on expiratory scan

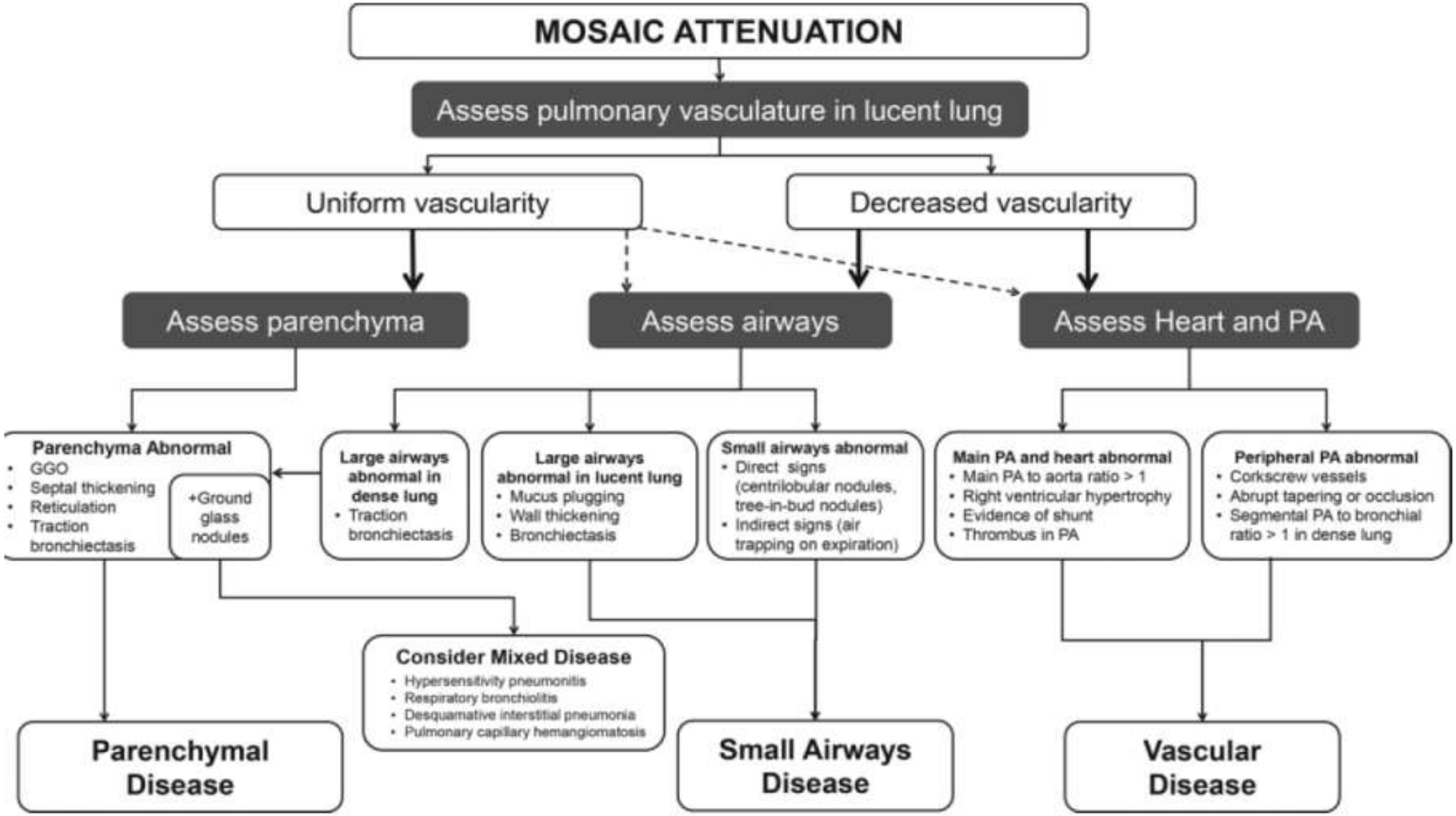


Monaldi Arch Chest Dis 2005; 63: 2, 108-110.

Causes of mosaic attenuation

Variable	Vessel Size	Inspiration/ Expiration CT Scanning
Small airways disease	Decreased size and number in lucent lung	Air trapping
Pulmonary vascular disease	Decreased size and number in lucent lung	No air trapping
Diffuse infiltrative disease	Similar size and number throughout lung	No air trapping

Raju S et al.,Chest. 2017 Jun;151(6):1356-1374



Kligerman et al., Radiographics. 2015 Sep-Oct;35(5):1360-80

RESEARCH Open Access

Paired inspiratory-expiratory chest CT scans to assess for small airways disease in COPD

Abstract

Background: Gas trapping quantified on chest CT scans has been proposed as a surrogate for small airway disease in COPD. We sought to determine if measurements using paired inspiratory and expiratory CT scans may be better able to separate gas trapping due to emphysema from gas trapping due to small airway disease.

Methods: Smokers with and without COPD from the COPDGene Study underwent inspiratory and expiratory chest CT scans. Emphysema was quantified by the percent of lung with attenuation < −950HU on inspiratory CT. Four gas trapping measures were defined: (1) Exp_{-856}, the percent of lung < −856HU on expiratory imaging; (2) E/I MLA, the ratio of expiratory to inspiratory mean lung attenuation; (3) $RVC_{856\text{-}950}$, the difference between expiratory and inspiratory lung volumes with attenuation between −856 and −950 HU; and (4) Residuals from the regression of Exp_{-856} on percent emphysema.

Results: In 8517 subjects with complete data, Exp_{-856} was highly correlated with emphysema. The measures based on paired inspiratory and expiratory CT scans were less strongly correlated with emphysema. Exp_{-856}, E/I MLA and $RVC_{856\text{-}950}$ were predictive of spirometry, exercise capacity and quality of life in all subjects and in subjects without emphysema. In subjects with severe emphysema, E/I MLA and $RVC_{856\text{-}950}$ showed the highest correlations with clinical variables.

Conclusions: Quantitative measures based on paired inspiratory and expiratory chest CT scans can be used as markers of small airway disease in smokers with and without COPD, but this will require that future studies acquire both inspiratory and expiratory CT scans.

Hersh et al. Respiratory Research 2013, 14:42

Paired inspiratory-expiratory chest CT scans to assess for small airways disease in COPD

Table 4 Correlations between gas trapping measures and quantitative outcomes in subjects with severe emphysema ($Insp_{-950HU}$ > 15% ex-smokers, $Insp_{-950HU}$ > 14% current smokers)

			Correlations			
	N	Mean (SD)	Exp_{-856}	E/I MLA	$RVC_{856-950}$	Residual
FEV_1 % predicted	1185	41.2 (19.9)	−0.69‡	−0.73‡	−0.73‡	−0.16‡
FVC % predicted	1185	75.7 (21.1)	−0.49‡	−0.56‡	−0.57‡	−0.17‡
FEV_1/FVC	1185	0.40 (0.12)	−0.66‡	−0.62‡	−0.62‡	−0.08*
FEF_{25-75}	1185	0.42 (0.38)	−0.56‡	−0.61‡	−0.61‡	−0.18‡
FRC/TLC ratio	1188	0.69 (0.12)	0.80*	0.93*	0.87*	0.44*
6MWD	1135	1116 (404)	−0.31‡	−0.40‡	−0.43‡	-0.01^{NS}
Exacerbation frequency	1188	0.8 (1.2)	0.10†	0.12‡	0.13‡	-0.02^{NS}
SGRQ total	1188	44.9 (19.9)	0.32‡	0.41‡	0.43‡	0.09*
MMRC dyspnea	1183	2.5 (1.3)	0.34‡	0.38‡	0.42‡	0.01^{NS}

Pearson correlation coefficients are shown.

Hersh et al. Respiratory Research 2013, 14:42

RESEARCH ARTICLE Open Access

Relationship between CT air trapping criteria and lung function in small airway impairment quantification

Abstract

Background: Small airways are regarded as the elective anatomic site of obstruction in most chronic airway diseases. Expiratory computed tomography (CT) is increasingly used to assess obstruction at this level but there is no consensus regarding the best quantification method. We aimed to evaluate software-assisted CT quantification of air trapping for assessing small airway obstruction and determine which CT criteria better predict small airway obstruction on single breath nitrogen test (SBNT).

Methods: Eighty-nine healthy volunteers age from 60 to 90 years old, underwent spirometrically-gated inspiratory (I) and expiratory (E) CT and pulmonary function tests (PFTs) using SBNT, performed on the same day. Air trapping was estimated using dedicated software measuring on inspiratory and expiratory CT low attenuation area (LAA) lung proportion and mean lung density (MLD). CT indexes were compared to SBNT results using the Spearman correlation coefficient and hierarchical dendrogram analysis. In addition, receiver operating characteristic (ROC) curve analysis was performed to determine the optimal CT air-trapping criterion.

Results: 43 of 89 subjects (48,3%) had dN2 value above the threshold defining small airway obstruction (i.e. 2.5% N2/I). Expiratory to inspiratory MLD ratio ($r = 0.40$) and LAA for the range −850 -1024 HU ($r = 0.29$) and for the range −850 -910 HU ($r = 0.37$) were positively correlated with SBNT results. E/I_{MLD} was the most suitable criterion for its expression. Expiratory to inspiratory MLD ratio (E/I_{MLD}) showed the highest AUC value (0.733) for small airway obstruction assessment.

Conclusion: Among all CT criteria, all correlating with small airway obstruction on SBNT, E/I_{MLD} was the most suitable criterion for its expression in asymptomatic subjects with mild small airway obstruction

Bommart et al. BMC Pulmonary Medicine 2014, 14:29

HRCT

- Unable to visualise small airways directly
- Specialist software may be required
- No standardised measurements
- Radiation dose

Hyperpolarised helium MRI

- Assessment of **distribution of ventilation and morphometry of the distal airways** and lung parenchyma
- No exposure to ionising radiation
- Diffusion imaging visualizes the movement of 3He in the peripheral airspaces, bound by alveolar and airways walls. This is calculated as the apparent **diffusion co-efficient (ADC)**
- Quantification of regional ventilation - achieved by both static and dynamic assessment of 3He distribution within the lung
- Largely restricted to research applications and its role in the clinical management of airways disease is not yet clear

McNulty W et al.. Eur Clin Respir J. 2014 Oct 17;1

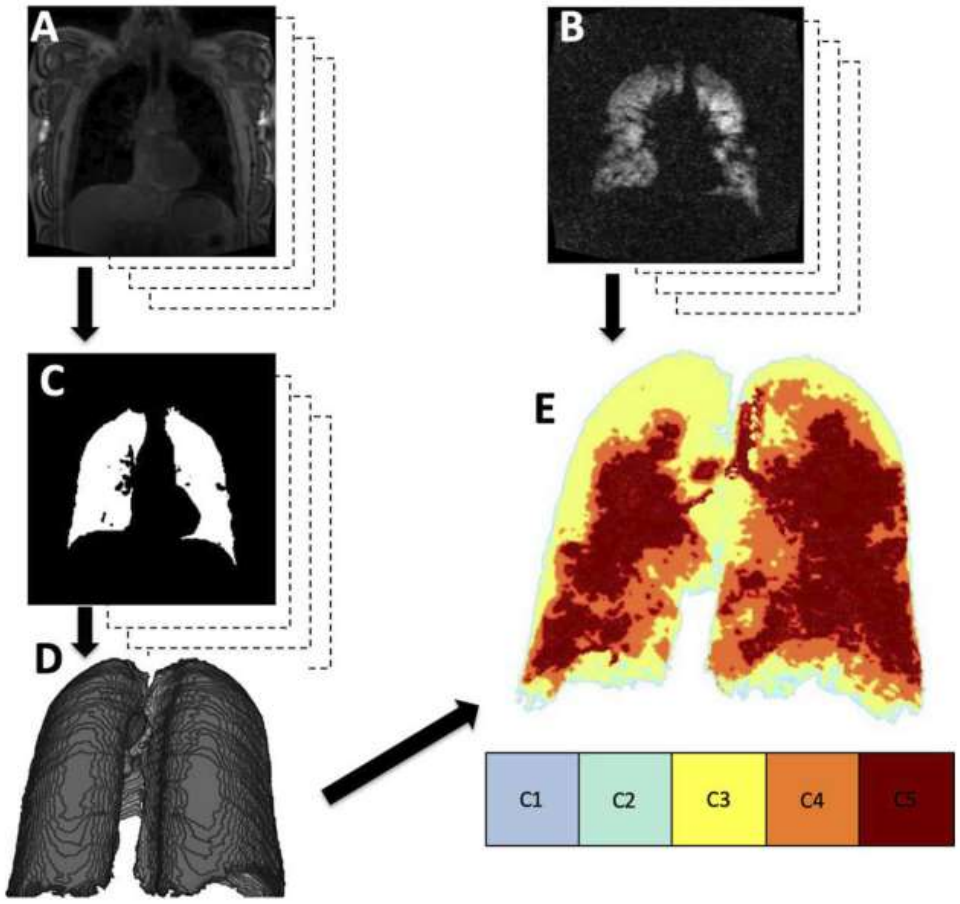
RESEARCH ARTICLE

Airway closure is the predominant physiological mechanism of low ventilation seen on hyperpolarized helium-3 MRI lung scans

Hyperpolarized helium-3 MRI (^{3}He MRI) provides detailed visualization of low- (hypo- and non-) ventilated lungs. Physiological measures of gas mixing may be assessed by multiple breath nitrogen washout (MBNW) and of airway closure by a forced oscillation technique (FOT). We hypothesize that in patients with asthma, areas of low-ventilated lung on ^{3}He MRI are the result of airway closure. Ten control subjects, ten asthma subjects with normal spirometry (non-obstructed), and ten asthmatic subjects with reduced baseline lung function (obstructed) attended two testing sessions. On visit one, baseline plethysmography was performed followed by spirometry, MBNW, and FOT assessment pre and post methacholine challenge. On visit two, ^{3}He MRI scans were conducted pre and post methacholine challenge. Post methacholine the volume of low-ventilated lung increased from 8.3% to 13.8% in the non-obstructed group ($P = 0.012$) and from 13.0% to 23.1% in the obstructed group ($P = 0.001$). For all subjects, the volume of low ventilation from ^{3}He MRI correlated with a marker of airway closure in obstructive subjects, Xrs (6 Hz) and the marker of ventilation heterogeneity Scond with r^2 values of 0.61 ($P < 0.001$) and 0.56 ($P < 0.001$), respectively. The change in Xrs (6 Hz) correlated well ($r^2 = 0.45$, $p < 0.001$), whereas the change in Scond was largely independent of the change in low ventilation volume ($r^2 = 0.13$, $P < 0.01$). The only significant predictor of low ventilation volume from the multi-variate analysis was Xrs (6 Hz). This is consistent with the concept that regions of poor or absent ventilation seen on ^{3}He MRI are primarily the result of airway closure.

Nilsen K,et al. J Appl Physiol (1985). 2021 Mar 1;130(3):781-791.

Hyperpolarized helium-3 MRI lung scans

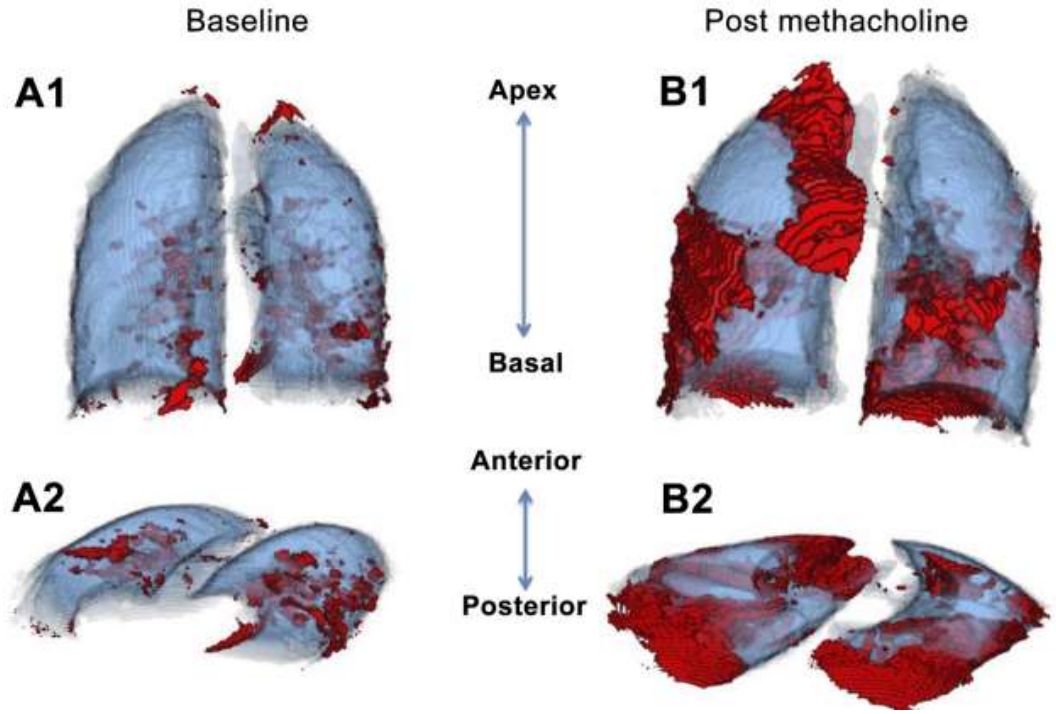


- Image clusters C1– C5 (dark to light) represent the different levels of ventilation (C1 = ventilation defect, C2–C5 = hypoventilation to hyperventilation

Nilsen K,et al. J Appl Physiol (1985). 2021 Mar 1;130(3):781-791.

Hyperpolarized helium-3 MRI lung scans

- A: 3He MRI scan pre methacholine
- B: post methacholine 3He MRI scan
- The red volumes represent the volume of low ventilation (image clusters C1 and C2)
- The transparent light blue volumes represent the image clusters 3-5



Nilsen K,et al. J Appl Physiol (1985). 2021 Mar 1;130(3):781-791.

Nuclear medicine techniques

- Two-dimensional gamma scintigraphy
- Single photon emission computed tomography (SPECT)
- Positron emission tomography (PET)

Two-dimensional (2-D) gamma scintigraphy

- Gamma-emitting radionucleides deposited within the lung can be imaged as they decay
- Used to assess the effect of particle size on deposition within the lungs
- 99mTc is more commonly used
- Total lung deposition and information on regional lung deposition
- Exposure to ionising radiation
- 2-D imaging does **not allow precise localisation of drug deposition** as both central and small airways as well as alveolar distribution may contribute to gamma counts for any given area
- Analysis of the left lung can be complicated by overlap of activity on the stomach when viewed in two dimensions

J. Conway et al. Advanced Drug Delivery Reviews 64 (2012) 357–368

Single photon emission computed tomography (SPECT)

- 3-D imaging modality using multiple gamma detectors that rotate around a supine patient
- SPECT can be used to image ventilation using either radiolabelled gasses or ultrafine particles (Technegas)
- Extent of regional distribution of airflow
- Technique can be combined with perfusion imaging to assess ventilation perfusion relationships in the lung
- Limitations of SPECT scanning -higher radiation doses to patients and a longer acquisition time
- Difficult to identify small airways

Crawford AB et al .Eur Respir J. 1990 Jun;3(6):686-92

Positron emission tomography (PET)

- Used to assess drug deposition, inflammation, and ventilation perfusion relationships in the lung
- PET scanners and the facilities to produce radioisotopes are expensive
- Produce higher resolution images than SPECT
- Targeting of radioisotopes to specific receptors and targets within the lung
- Difficult to identify small airways

McNulty W et al.. Eur Clin Respir J. 2014 Oct 17;1

Histopathology

- Histopathological analysis of small airways disease
- Surgical lung biopsy -examination of multiple small airways
- Transbronchial biopsy -samples small numbers of airways.

Small airway disease

Clinical Classification of the Bronchiolar Diseases

Airway diseases

- Acute and chronic bronchiolitis
- Respiratory bronchiolitis
- Follicular bronchiolitis
- Diffuse panbronchiolitis
- Bronchiolitis obliterans

Interstitial diseases

- Respiratory bronchiolitis–interstitial lung disease (RB-ILD)
- Bronchiolitis obliterans organizing pneumonia (BOOP)

Bronchiolitis obliterans- two types of lesions are proliferative bronchiolitis and constrictive bronchiolitis depending on severity obliteration of the bronchioles (the obliterans term) may or may not occur with these lesions

Clinical Classification of Bronchiolitis Obliterans

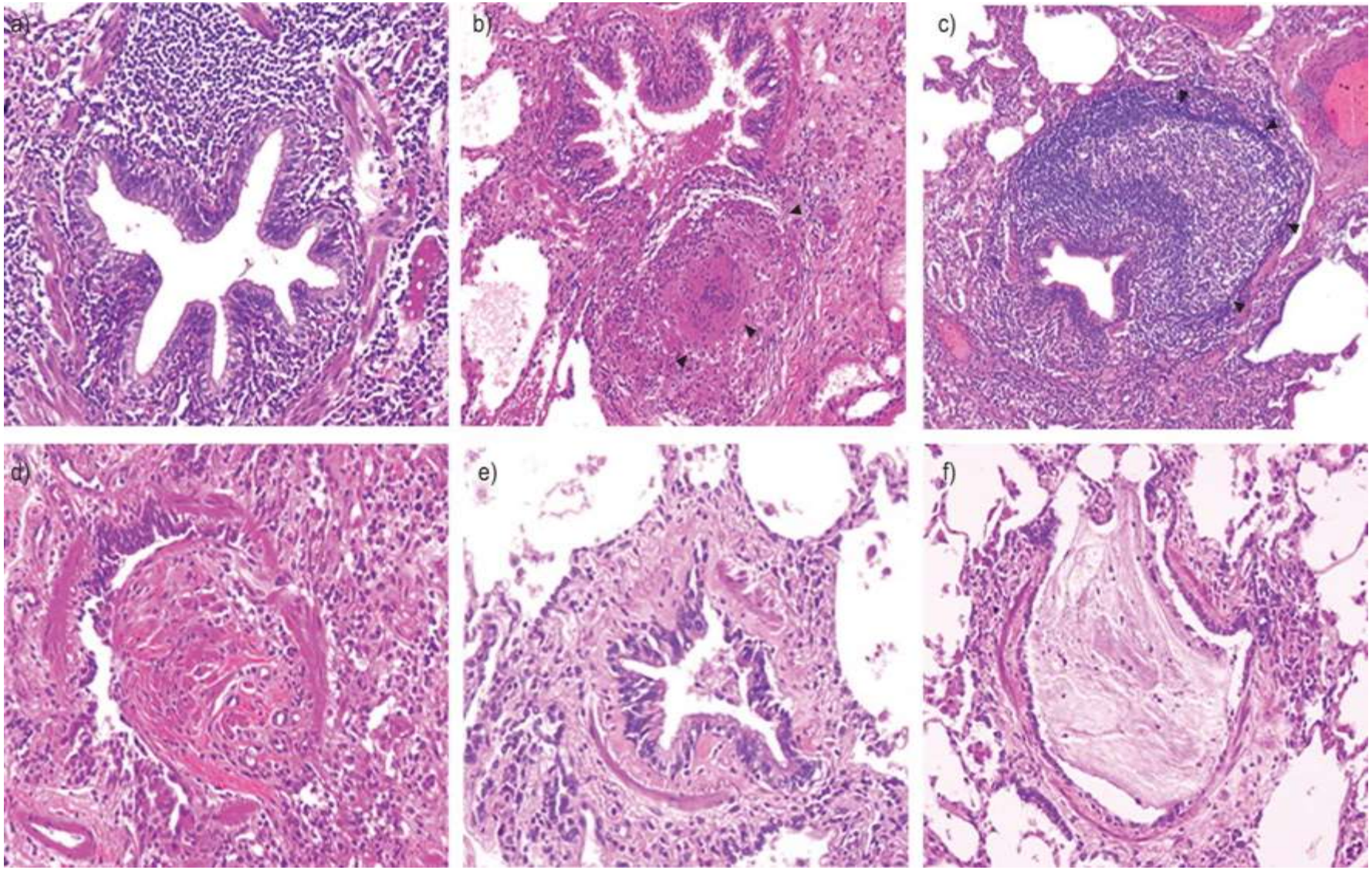
Idiopathic
Toxic fumes
Post–respiratory infections
Connective tissue disorders
Drug-related
Organ transplantation
- Bone marrow and stem cell
- Lung

Aspiration
Neuroendocrine hyperplasia with carcinoid
Sauropus androgynous
Miscellaneous system diseases
- Stevens–Johnson syndrome
- Paraneoplastic pemphigus
- Primary biliary cirrhosis
- Swyer–James syndrome
- Ataxia telangiectasia
- Inflammatory bowel disease

Histological classification of bronchiolar disorders	
Primary bronchiolar disorders	• Constrictive bronchiolitis (obliterative bronchiolitis and bronchiolitis obliterans) • Acute bronchiolitis • Diffuse panbronchiolitis • Respiratory bronchiolitis (smoker's bronchiolitis) • Mineral dust airway disease • Follicular bronchiolitis • Other primary bronchiolar disorders, e.g. diffuse aspiration bronchiolitis and lymphocytic bronchiolitis
ILD with a prominent bronchiolar involvement	• Hypersensitivity pneumonitis • Respiratory bronchiolitis-associated interstitial lung disease Cryptogenic organising pneumonia • Other interstitial lung disease (PLCH, sarcoidosis and bronchiolocentric interstitial pneumonia)
Bronchiolar involvement in diseases also involving large airways	• Chronic obstructive pulmonary disease • Bronchiectasis, including cystic fibrosis • Asthma

Burgel PR et al.Eur Respir Rev 2013; 22: 128, 131–147

Surgical lung biopsy in patients with bronchiolitis



a) Cellular bronchiolitis
b) Granulomatous bronchiolitis
c) Follicular bronchiolitis
d) Bronchiolitis obliterans with a fibro-inflammatory polyp
e) Obliterative (constrictive) bronchiolitis
f) Mucous plugging

Pierre-Régis Burgel et al. Eur Respir Rev 2013;22:131-147

Transbronchial Cryobiopsy Can Diagnose Constrictive Bronchiolitis in Veterans of Recent Conflicts in the Middle East

Table 1. Demographic Data, Noninvasive Evaluations, and Cryobiopsy Results

	Patient 1	Patient 2	Patient 3	Patient 4
Age, yr	48	33	42	26
Sex	Male	Male	Male	Male
Race	White	White	White	White
Smoking	Never	Never	Never	Never
Service theater	Iraq	Iraq	Afghanistan	Iraq and Afghanistan
Exposures during service	Burn pits	Burn pits, combat smoke	Burn pits	Burn pits
History of respiratory disease	No	No	No	No
HRCT chest	Normal	3-mm nodule	Right middle lobe bronchial thickening	Air trapping, mild
PFT pattern	Restriction	Normal	Normal	Mixed obstruction/restriction
FEV_1, % predicted	71	94	81	66
FVC, % predicted	76	89	78	78
TLC, % predicted	76	100	80	64
D_{LCO}, % predicted	95	108	92	97
CPET pattern	Not performed	No cardiac limitation	Not performed	Not performed
Cryobiopsy diagnostic of CB	No	Yes	Yes	Yes

Lentz RJ, et al. Am J Respir Crit Care Med. 2016 Apr 1;193(7):806-8

Cryobiopsy in the diagnosis of bronchiolitis: a retrospective analysis of twenty-three consecutive patients

Bronchiolitis manifests as a variety of histological features that explain the complex clinical profiles and imaging aspects. In the period between January 2011 and June 2015, patients with a cryobiopsy diagnosis of bronchiolitis were retrospectively retrieved from the database of our institution. Clinical profiles, imaging features and histologic diagnoses were analysed to identify the role of cryobiopsy in the diagnostic process. Twenty-three patients with a multidisciplinary diagnosis of small airway disease were retrieved (14 females, 9 males; age range 31–74 years old; mean age 54.2 years old). The final MDT diagnoses were post-infectious bronchiolitis (n = 5), constrictive bronchiolitis (n = 3), DIPNECH (n = 1), idiopathic follicular bronchiolitis (n = 3), Sjogren's disease (n = 1), GLILD (n = 1), smoking-related interstitial lung disease (n = 6), sarcoid with granulomatous bronchiolar disorder (n = 1), and subacute hypersensitivity pneumonitis (n = 2). Complications reported after the cryobiopsy procedure consisted of two cases of pneumothorax soon after the biopsy (8.7%), which were successfully managed with the insertion of a chest tube. Transbronchial cryobiopsy represents a robust and mini-invasive method in the characterization of small airway diseases, allowing a low percentage of complications and good diagnostic confidence.

*Sirol et al. Sci Rep **10**, 10906 (2020)*

Approach to case of small airway disease

History and clinical examination

- Progressive dyspnoea , predominantly dry cough (DBP-copious expectoration) , exercise desaturation+/- , signs of hyperinflation or normal examination , history of CTD/long term drug intake/post infections / post transplant/ GERD / radiation exposure/ chronic aspiration/ fumes and toxins exposure

Chest x ray / PFT / blood investigations

- CTD workup/ HIV/ immunodeficiency workup

HRCT chest inspiratory and expiratory scans

- Direct and indirect sings of small airway involvement

MDD

Lung biopsy

Conclusion

- PFT-Fixed cut-off is not available ,LLN is not available
- None of the physiological and radiological investigation is specific for small airway disease
- Lung biopsy is need for definitive diagnosis
- Most of the investigations are not standardised
- Most of them are research based investigation
- Multidisciplinary approach is needed to make diagnosis of small airway disease