Approach To Bronchiolar Disorders

DM Seminar

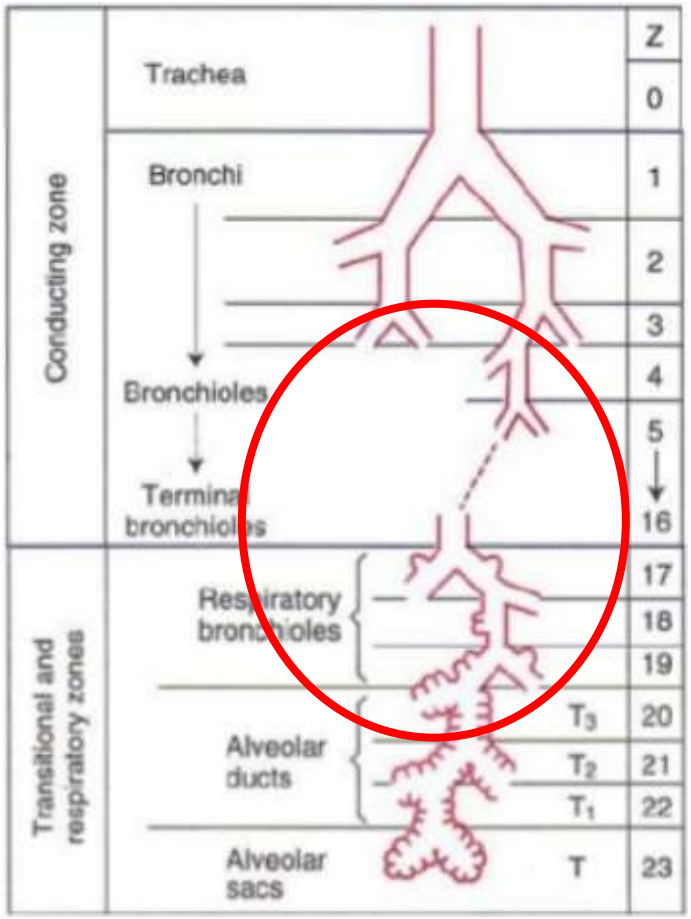
Dr Srikant K M

31/07/20

Topics to be discussed

- Bronchiole anatomy and physiology
- Classification of bronchiolar disorders
- Clinical, Physiological and Radiological assessment of bronchiolar disorders
- Individual bronchiolar disorders and management
- Algorithm for approach to bronchiolar disorders
- Conclusion

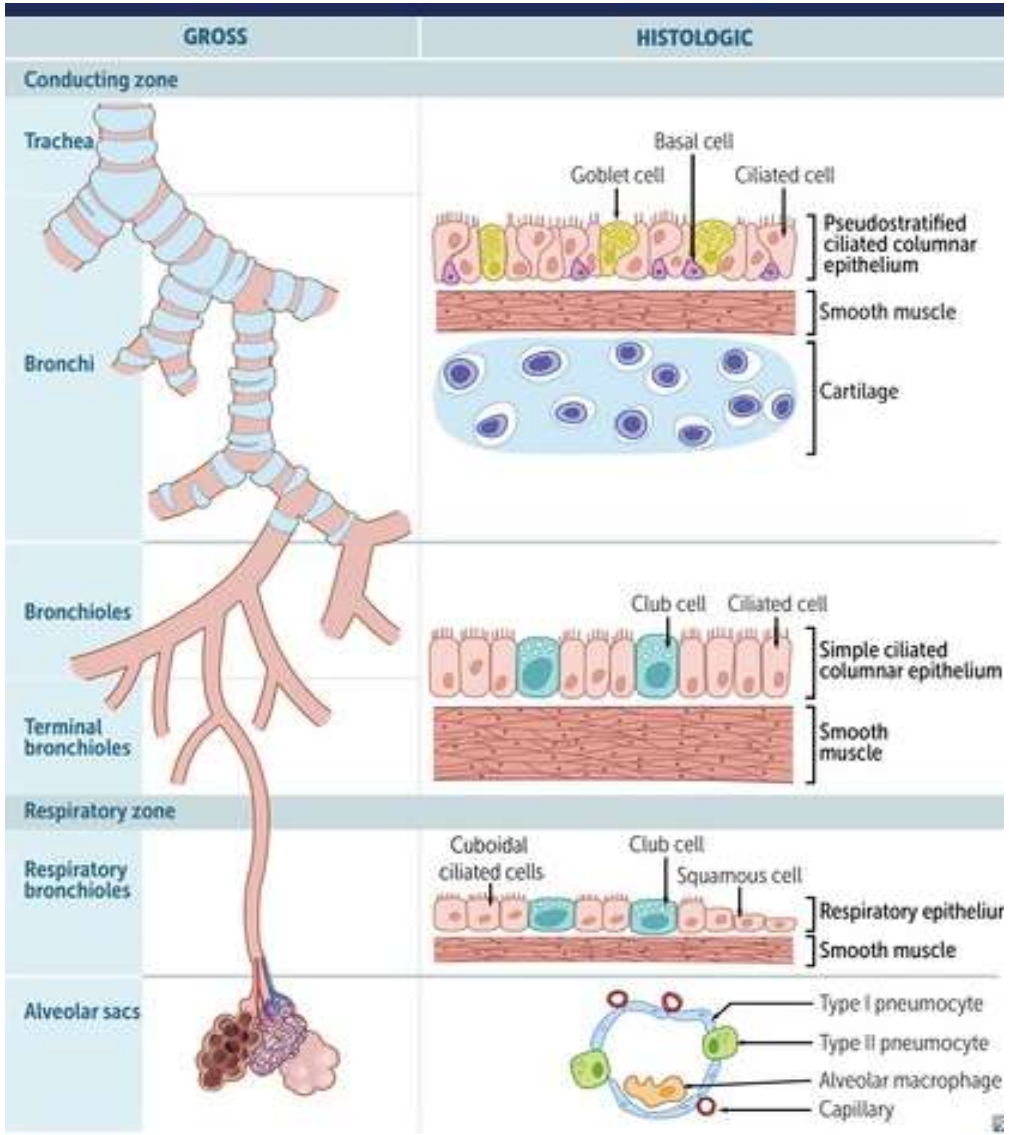
Bronchioles : Anatomy



- Small airways of internal diameter 2mm or less
- Extend from eight generation of conducting airways till respiratory bronchioles

C Ravaglia et al., Semin Respir Crit Care Med 2020

Bronchiole : Histology

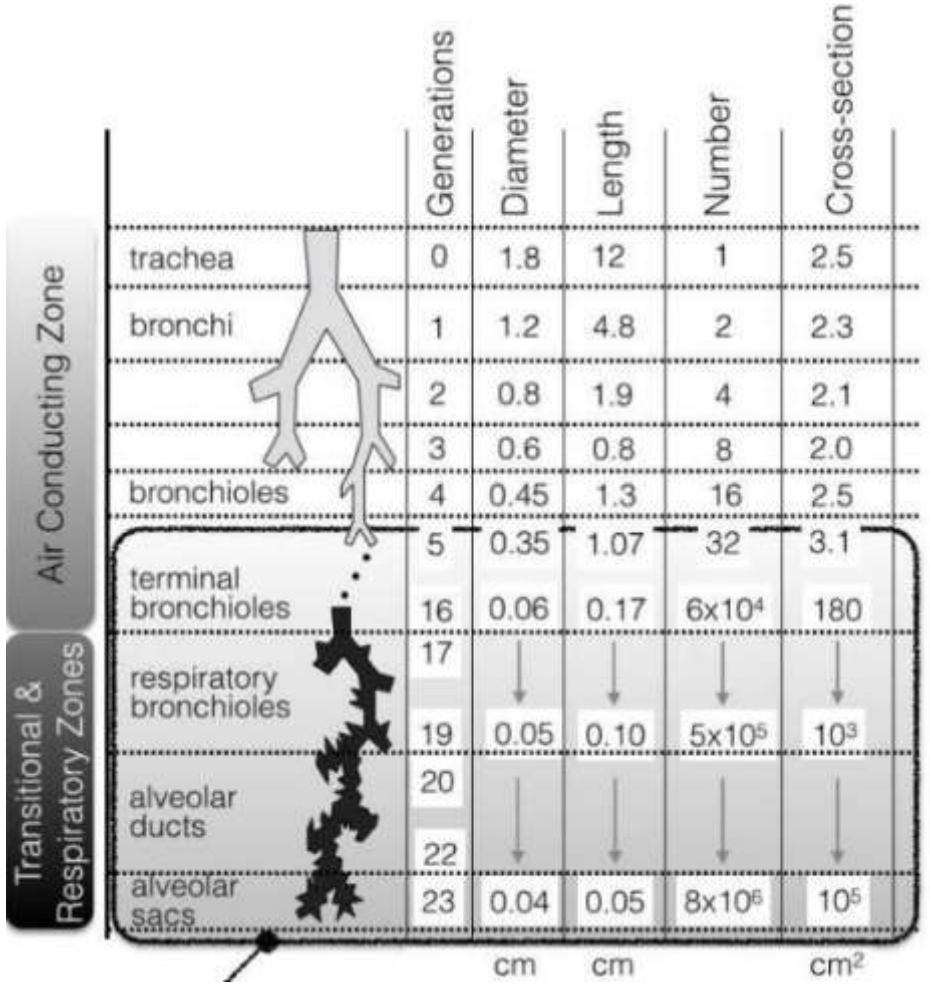


- Lack cartilage and mucus glands
- Are lined by surfactant which reduces surface tension

C Ravaglia et al., Semin Respir Crit Care Med 2020

Large Airways v/s Small Airways

	Large airway	Small airway
Cartilage and Mucus glands	+	-
Cross sectional Area	Lesser	Greater
Flow	Turbulent	Laminar
Resistance affected by gas density	+	-
Surfactant lining	-	+



Peter Macklem, AJRCCM 1998

Bronchiolar disorders- importance?

- Confusing Terminology
- Multiple classifications
- Non specific/disproportionate symptoms
- Diverse histopathological and radiological presentation
- Difficult assessment

Terminology

Synonyms

Bronchiolar disorders = Small airway disease = Peripheral airway disease

Obliterative bronchiolitis = Constrictive bronchiolitis

Similar terms different meaning

Bronchiolitis obliterans ≠ Bronchiolitis obliterans syndrome

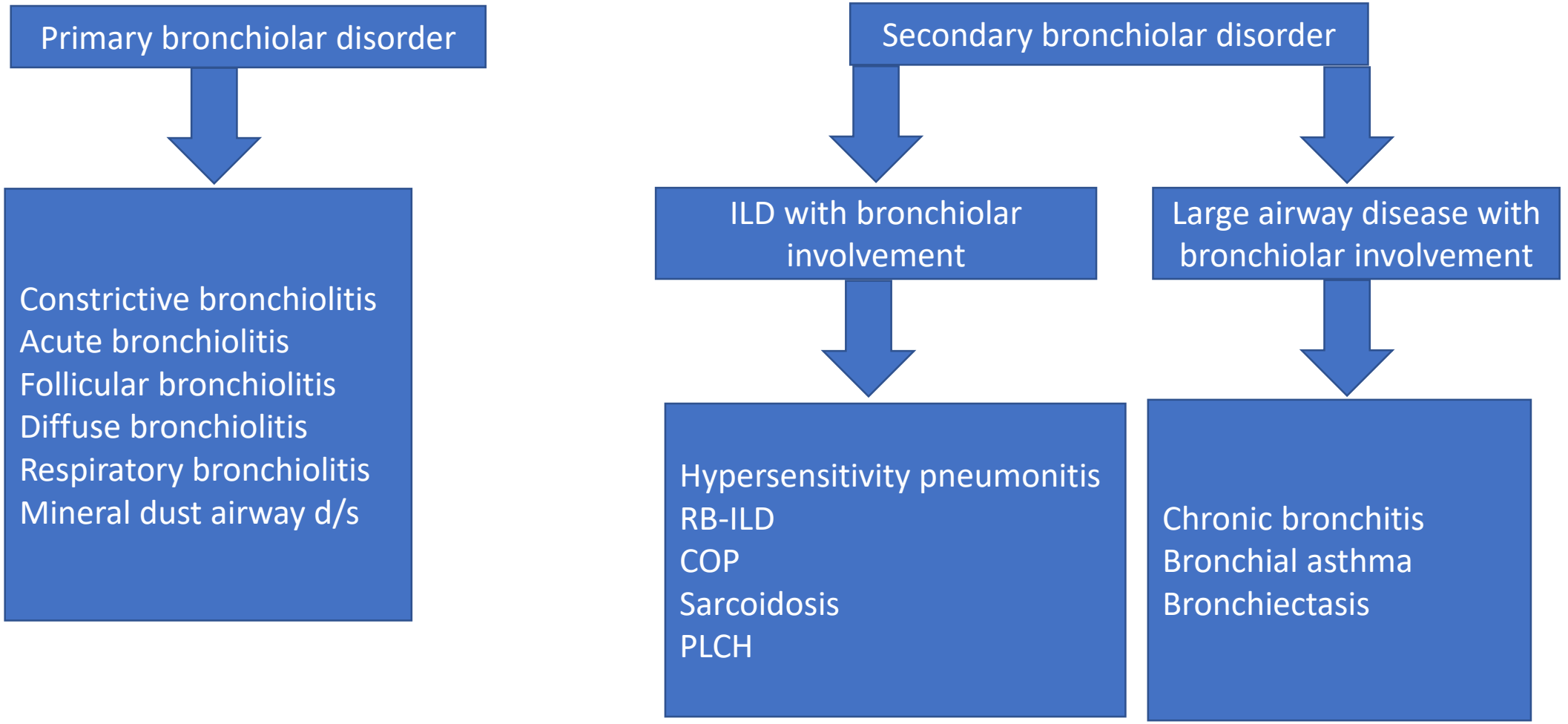
Bronchioles : Silent/Quiet zone
Difficult to assess

- Routine pulmonary function test fail to pick up bronchiole involvement at an early stage
- Bronchioles (<2mm) are beyond the resolution of HRCT chest
- Due to patchy involvement, bronchiole involvement may be missed on TBLB

J Mead et al.,N Engl J Med 1970

Peter Macklem, AJRCCM 1998

Classification of Bronchiolar Disorders



C Ravaglia et al., Semin Respir Crit Care Med 2020

Etiological Classification Of Bronchiolar Disorders

Classification
Inhalation Bronchiolitis (NO2, SO2, Diacetyl, chemical and incinerator fly ash)
Infectious and Postinfectious Bronchiolitis (viral, mycoplasma, mycobacterial)
Post transplant associated Bronchiolitis (HSCT, lung transplant)
CTD associated Bronchiolitis (RA, Sjogren's syndrome)
Drug Induced Bronchiolitis (Busulfan, gold, penicillamine)
Cryptogenic forms
Miscellaneous (paraneoplastic pemphigus, Diffuse idiopathic NE cell hyperplasia)

C Ravaglia et al.,Semin Respir Crit Care Med 2020

Histopathological Classification of Bronchiolar disorders

Classification
Cellular Bronchiolitis • Acute/neutrophilic or Chronic/Lymphocytic (Based on cell type) • Granulomatous or Follicular (Based on organisation of cells)
Proliferative bronchiolitis
Constrictive bronchiolitis
Peribronchiolar fibrosis and bronchiolar metaplasia

C Ravaglia et al.,Semin Respir Crit Care Med 2020

When to suspect a bronchiolar disorder ?

History and Clinical Features (Non Specific)

- Respiratory symptoms – cough and dyspnoea (acute/insidious onset)

- History pertinent to aetiology

  CTD(RA and Sjogren's synd.)

  Drug history(d- penicillamine, busulfan and gold)

  Exposure history – inhalational occupational/environmental/smoking

  Organ transplant

- Abnormal physical examination – normal/wheeze/crackles

Bronchiolar disorders – Chest radiograph

- Normal or
- Non specific findings – Hyperinflation/Nodular or reticulonodular opacities

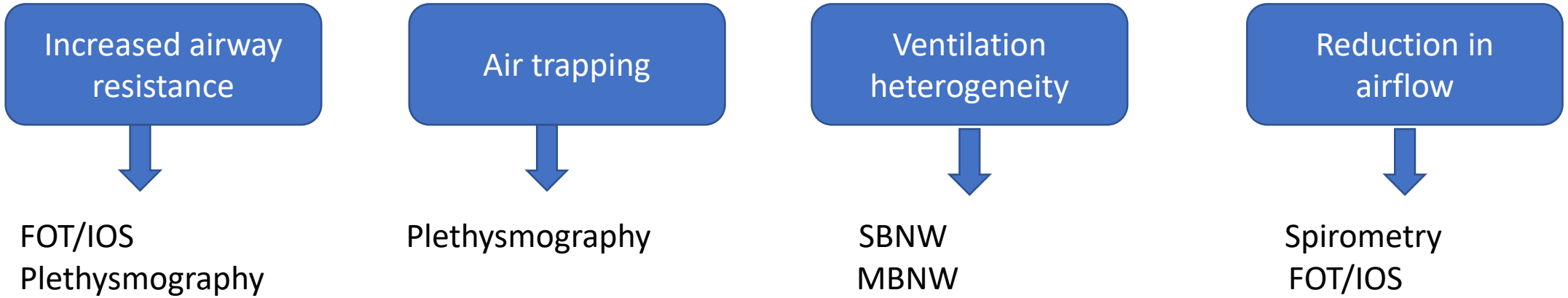
Bronchiolar disorders - PFTs

Spirometry (Non specific)

- Normal
- Obstructive pattern – constrictive bronchiolitis
- Restrictive pattern – RB, RBILD, BOOP, HP

Basis for Physiological Assessment of Small Airways

- Small airway dysfunction leads to reduction in airflow and increase in airway resistance
- Earlier closure results in Air trapping and abnormal distribution of ventilation



Macklem et al ., Am J Respir Crit Care Med 1998

Assessment of bronchiolar disorders - Spirometry – Role of $FEF_{25-75\%}$

- FEV1 reflects large airway obstruction
- MMEF($FEF_{25-75\%}$) postulated as indicator for small airway disease(reduced)[1]
- Studies show $FEF_{25-75\%}$ to be falsely normal in documented airflow limitation[2]
- Also less reproducible and correlate poorly with other markers of small airway disease such as air trapping or histological evidence of small airway inflammation[1]
- FVC dependent, changes with change in lung volume

1.Mcnulty et al., EUR Clin Respir J. 2014
2.Hansen JE et al ., CHEST 2006

Assessment of bronchiolar disorders – Role of FEF 25-75%

Asthma diagnosis and treatment

Physiologic correlates of distal lung inflammation in asthma

E. Rand Sutherland, MD, MPH, Richard J. Martin, MD, Russell P. Bowler, MD, PhD, Yujun Zhang, PhD, Michael D. Rex, BS, and Monica Kraft, MD *Denver, Colo*

Background: The distal lung is an important site of inflammation in asthma. Maximal midexpiratory flows and the ratio of maximal:partial flows are purported to reflect distal lung function.
Objective: We obtained contemporaneous transbronchial biopsy, spirometry, and plethysmography to describe more accurately the relationship between physiology and distal lung inflammation in asthma.

Abbreviations used
FEF_{25-75}: Forced expiratory flow at 25% to 75% of forced vital capacity
FVC: Forced vital capacity
M:P: Maximal:partial
V_s: Volume of inflammatory cells per surface area of alveolar tissue

- Poor correlation with histologically evident small airway inflammation

Sutherland et al., American Academy of Allergy, Asthma and Immunology, 2004

Assessment of bronchiolar disorders – Role of FEF 25-75%

Discriminating Measures and Normal Values for Expiratory Obstruction*

James E. Hansen, MD; Xing-Guo Sun, MD; and Karlman Wasserman, PhD, MD

Objectives: To develop mean and 95% confidence limits for the lower limit of normal (LLN) values for forced expiratory volume in 3 s (FEV_3)/FVC ratio for Latin, black, and white adults; to ascertain comparative variability of the FEV_1/FVC ratio, the FEV_3/FVC ratio, and forced expiratory flow, midexpiratory phase (FEF_{25-75}) in never-smoking adults; to evaluate their utility in measuring the effect of smoking on airflow limitation; and to develop and use the fraction of the FVC that had not been expired during the first 3 s of the FVC (1 − FEV_3/FVC) to identify the growing fraction of long-time-constant lung units.

Design: Analysis of the Third National Health and Nutrition Examination Survey (NHANES III) database of never-smokers and current smokers.

Participants: A total of 5,938 adult never-smokers and 3,570 current smokers from NHANES III with spirometric data meeting American Thoracic Society standards.

Measurements and results: After establishing new databases for never-smokers and current smokers, we quantified the mean and LLN values of FEV_3/FVC in never-smokers, and identified spirometric abnormalities in current smokers. When associated with older age, FEV_3/FVC decreases and 1 − FEV_3/FVC increases as FEV_1/FVC decreases. On average, using these measurements, the condition of current smokers worsened about 20 years faster than that of never-smokers by middle age. If < 80% of the mean predicted FEF_{25-75} was used to identify abnormality, over one quarter of all never-smokers would have been falsely identified as being abnormal. Using 95% confidence limits, 42% of 683 smokers with reduced FEV_1/FVC and/or FEV_3/FVC would have been judged as normal by FEF_{25-75}.

Conclusions: FEV_1/FVC, FEV_3/FVC, and 1 − FEV_3/FVC characterize expiratory obstruction well. In contrast, FEF_{25-75} measurements can be misleading and can cause an unacceptably large number of probable false-negative results and probable false-positive results.

(CHEST 2006; 129:369–377)

- High false negative rates

Hansen JE et al ., CHEST 2006

Assessment of bronchiolar disorders - Plethysmography

Residual volume is an important measure of small airway dysfunction indicates air trapping

Measurement of RV and RV/TLC is a useful marker of air trapping and hyperinflation

Airway resistance can be measured at mouth using volume and pressure

However is not specific for small airway disease, effort dependent and time consuming

Mcnulty et al., EUR Clin Respir J. 2014

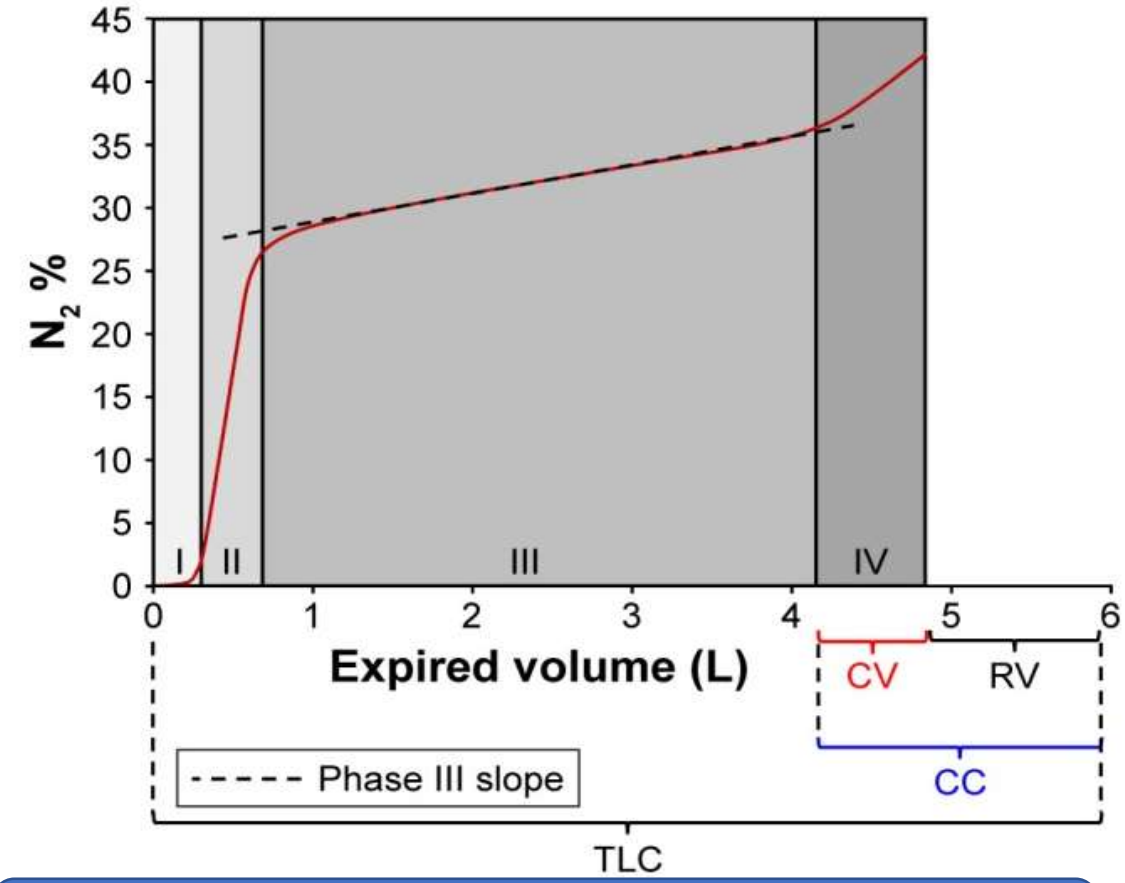
Physiological assessment of bronchiolar disorders

Single breath nitrogen washout

- Involves inhaling 100% oxygen from RV to TLC
- Exhaled volume of gas and N2 concentration are plotted on a graph
- Airway disease cause increase in slope of phase III of SBNW curve
- Airway disease cause increase in CV and CC
- However not specific for small airway disease

Mcnulty et al., Eur Clin Respir J. 2014

Single Breath Nitrogen Washout



- Phase I Dead space
- Phase II Dead space + alveoli
- Phase III Alveoli

Slope of Phase III heterogeneity in ventilation

- Phase IV Beginning of small a/w closure

Earlier Phase IV – air trapping, inc. RV

Has poor within individual reproducibility

Mcnulty et al., Eur Clin Respir J. 2014

Single Breath Nitrogen Washout

Does the nitrogen single-breath washout test contribute to detecting pulmonary involvement in rheumatoid arthritis? A pilot study

Elizabeth Jauhar Cardoso Bessa[1], Felipe de Miranda Carbonieri Ribeiro[2], Geraldo da Rocha Castelar Pinheiro[1] and Agnaldo José Lopes[1,3,4*]

Abstract

Objective: There has been growing interest in studying small airway disease through measures of ventilation distribution, thanks to the resurgence of the nitrogen single-breath washout (N_2SBW) test. Therefore, this study evaluated the contribution of the N_2SBW test to the detection of pulmonary involvement in patients with rheumatoid arthritis (RA).

Results: Twenty-one patients with RA underwent clinical evaluation, pulmonary function tests (PFTs), including the $N2_5$BW test, and computed tomography (CT). The main tomographic findings were air trapping and bronchiectasis (57.1% and 23.8% of cases, respectively). According to the phase III slope of the N_2SBW (phase III slope), 11 and 10 patients had values < 120% predicted and > 120% predicted, respectively. Five patients with limited involvement on CT had a phase III slope > 120%. The residual volume/total lung capacity ratio was significantly different between patients with phase III slopes < 120% and > 120% ($P = 0.024$). Additionally, rheumatoid factor positivity was higher in patients with a phase III slope > 120% ($P = 0.021$). In patients with RA and airway disease on CT, the N_2SBW test detects inhomogeneity in the ventilation distribution in approximately half of the cases, even in those with normal conventional PFT results.

Keywords: Rheumatoid arthritis, Pulmonary function test, Small airway disease, Computed tomography

In 21 patients of RA with predominant airway involvement(80%)
SBNW was able to detect ventilation heterogeneity in approximately half of the cases

Bessa et al., BMJ. 2019

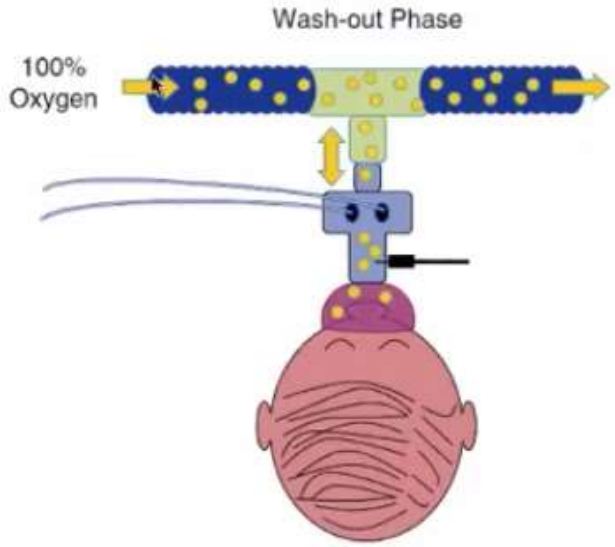
Physiological assessment of bronchiolar disorders
Multiple Breath Nitrogen Washout

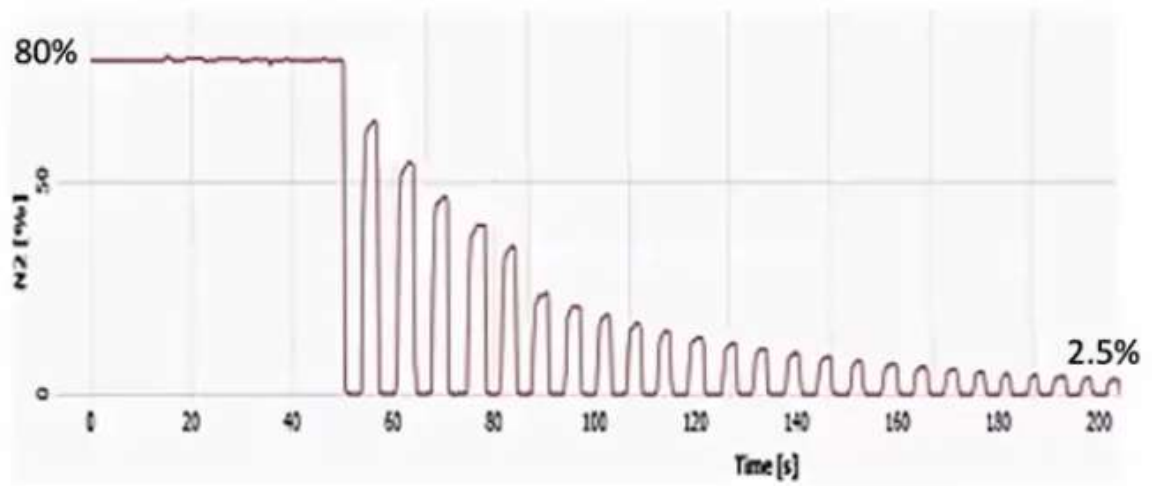
- Involves inhaling 100% O2 from FRC at fixed tidal volume and rate
- Test continues till N2 concentration in exhaled breath is <2.5%
- Speed and efficiency of gas mixing are dependent on tidal volume, frequency and ventilation heterogeneity

Mcnulty et al., Eur Clin Respir J. 2014

Physiological assessment of bronchiolar disorders
Multiple Breath Nitrogen Washout

N_2 MBW Technique



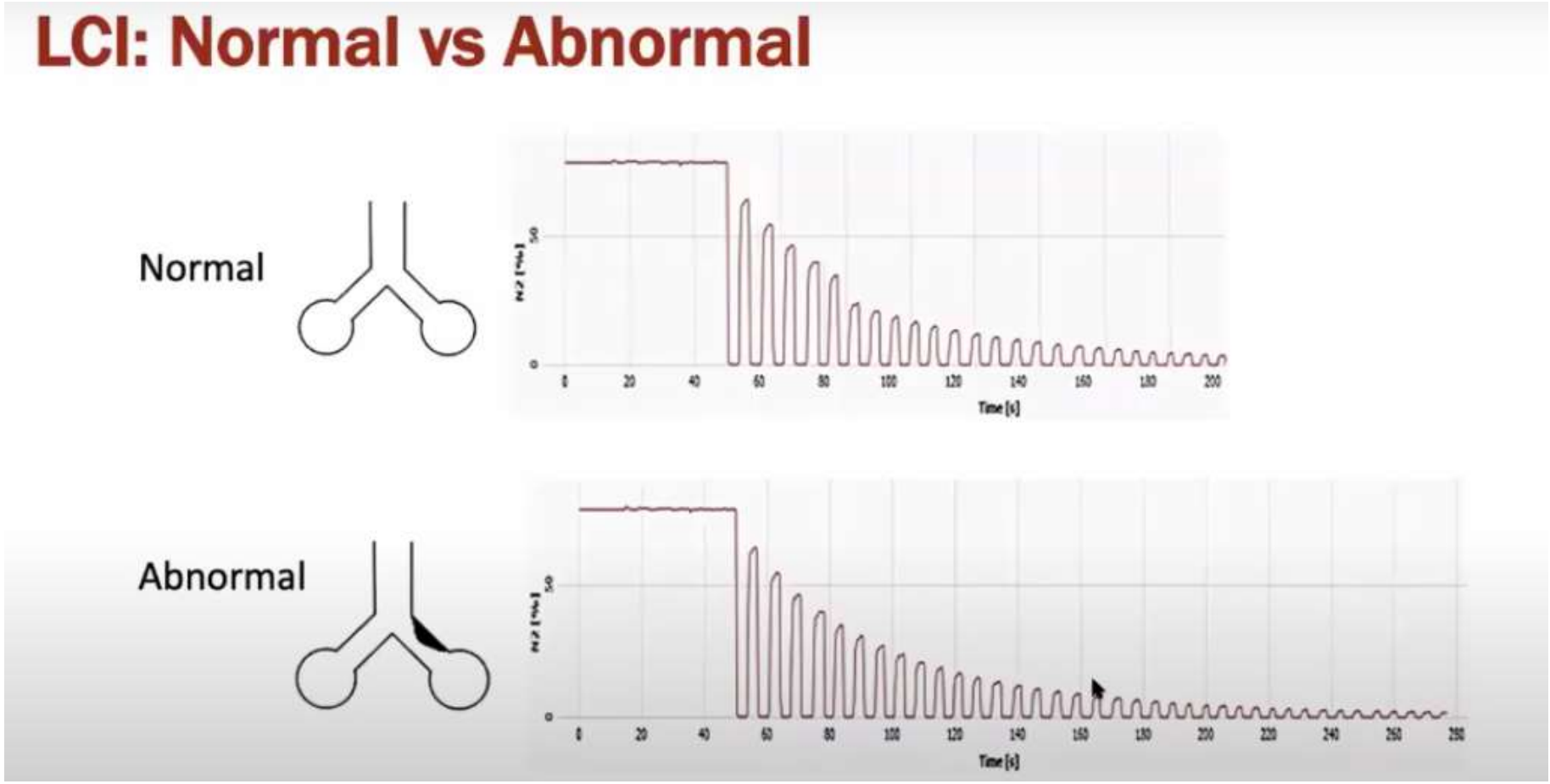


Multiple Breath Nitrogen Washout

- LCI is used as a measure of efficiency of gas mixing
- LCI is defined as number of FRC equivalents required to bring the tracer gas concentration in exhaled breath to <2.5%
- LCI is directly proportional to ventilation heterogeneity

Mcnulty et al., Eur Clin Respir J. 2014

Multiple Breath Nitrogen Washout



FRC = Volume of inert gas/F trace initial – F trace final

LCI = Cumulative expired volume/ FRC

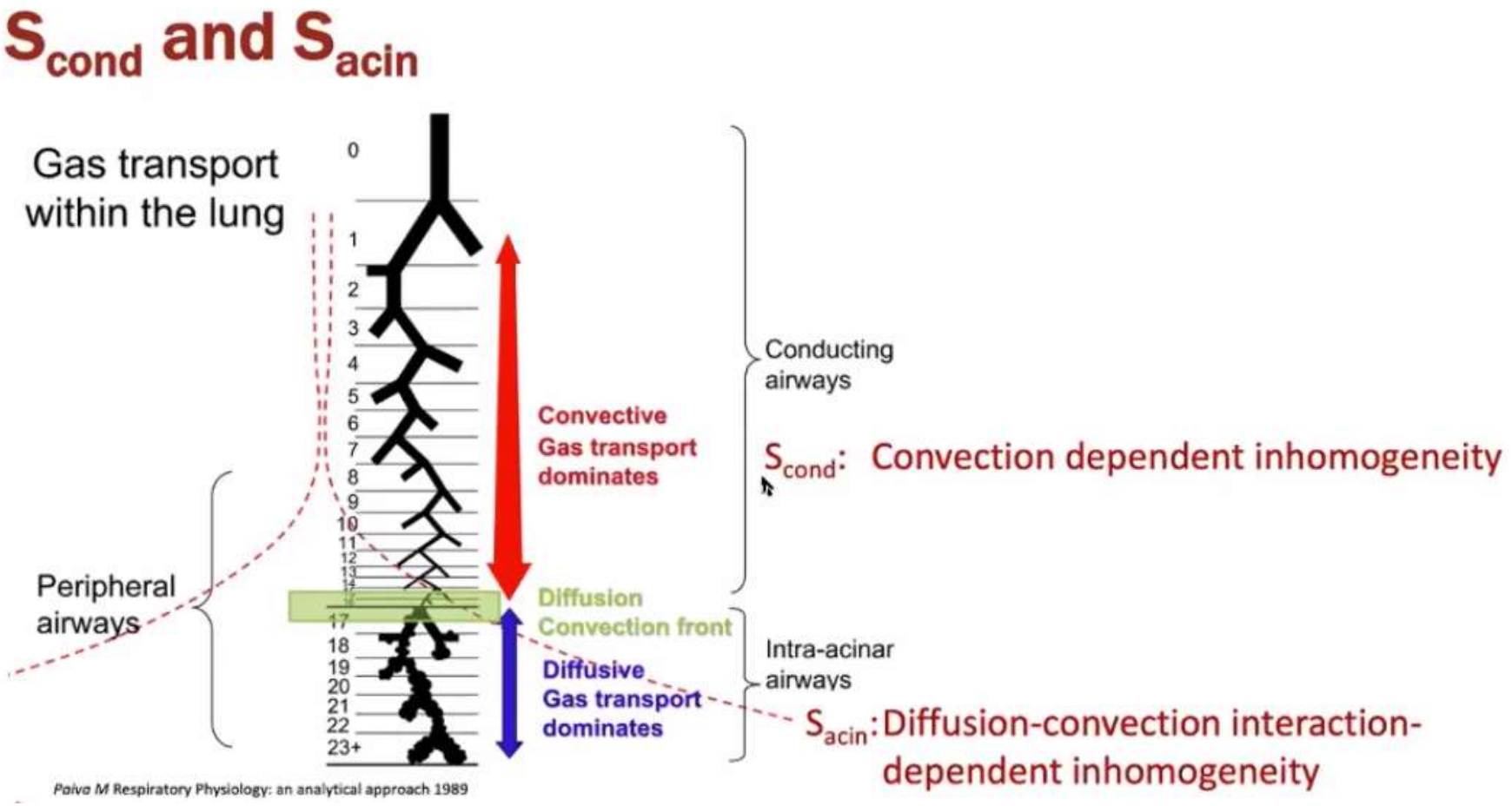
Mcnulty et al., Eur Clin Respir J. 2014

Multiple Breath Nitrogen Washout
Localizing site of ventilation heterogeneity

- Slope of phase III in MBNW changes in every breath
- This slope is normalized for mean expired nitrogen concentration
- During initial phases this slope depends on diffusion convection(DCDI) and later just on convection(CDI)
- The quantification of CDI component S_{cond} and DCDI component S_{acin} can help in locating site of pathology

Mcnulty et al., Eur Clin Respir J. 2014

Multiple Breath Nitrogen Washout



Mcnulty et al., Eur Clin Respir J. 2014

Physiological assessment of small airways- MBW in BOS

ORIGINAL ARTICLE
BRONCHIOLITIS OBLITERANS SYNDROME

Lung clearance index in detection of post-transplant bronchiolitis obliterans syndrome

Madeleine Driskel[1,2], Alex Horsley[3], Laurice Fretwell[4], Nigel Clayton[1] and Mohamed Al-Aloul[2]

Affiliations: [1]Lung Function Laboratory, Manchester University NHS Foundation Trust, Manchester, UK. [2]Cardiothoracic Transplant Unit, Manchester University NHS Foundation Trust, Manchester, UK. [3]Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK. [4]School of Human Sciences, University of Derby, Derby, UK.

ABSTRACT

Background: Long-term outcomes after lung transplantation are often limited by the development of obliterative bronchiolitis (OB), which is clinically defined using spirometry as bronchiolitis obliterans syndrome (BOS). Lung clearance index (LCI), derived from multiple breath washout (MBW) testing, is a global measure of ventilation heterogeneity that has previously been shown to be a more sensitive measure of obstructive small airway diseases than spirometry. We aimed to assess the feasibility of LCI in adult lung transplant patients and to compare LCI to BOS grade.

Methods: 51 stable adult double-lung transplant recipients performed sulfur hexafluoride MBW in triplicate on a single occasion, using a closed-circuit Innocor device. BOS grades were derived from serial spirometry according to International Society for Heart and Lung Transplantation criteria and, where available, high-resolution computed tomography (HRCT) evidence of OB was recorded.

Results: LCI was successfully performed in 98% of patients. The within-visit coefficient of variation for repeat LCI measurements was 3.1%. Mean LCI increased significantly with BOS grades: no BOS (n=15), LCI 7.6; BOS-0p (n=16), LCI 8.3; BOS-1 (n=11), LCI 9.3; BOS-2–3 (n=9), LCI 13.2 ($p<0.001$). 27 patients had HRCT within 12 months. LCI in those with HRCT evidence of OB was higher than those without OB (11.1 *versus* 8.2, p=0.006). 47% patients displayed abnormal LCI (>7) despite a normal forced expiratory volume in 1 s (FEV_1) (>80% of baseline).

Conclusions: LCI measurement in lung transplant recipients is feasible and reproducible. LCI increased with increasing BOS grade. A significant proportion of this cohort had abnormal LCI with preserved FEV_1, suggesting early subclinical small airway dysfunction, and supporting a role for MBW in the early identification of BOS.

Driskel et al., et al., ERJ 2019

Physiological assessment of bronchiolar disorders – Forced Oscillation Technique / IOS

- Use of sound waves superimposed on tidal breathing to measure mechanical properties of lung
- Mechanical properties are represented by resistance and reactance
- Resistance at higher frequencies 20Hz indicate contribution of proximal airway
- Resistance at lower frequencies 5Hz indicate contribution of whole lung
- Difference b/w R20 and R5 (R5-R20) indicates resistance offered by small airways

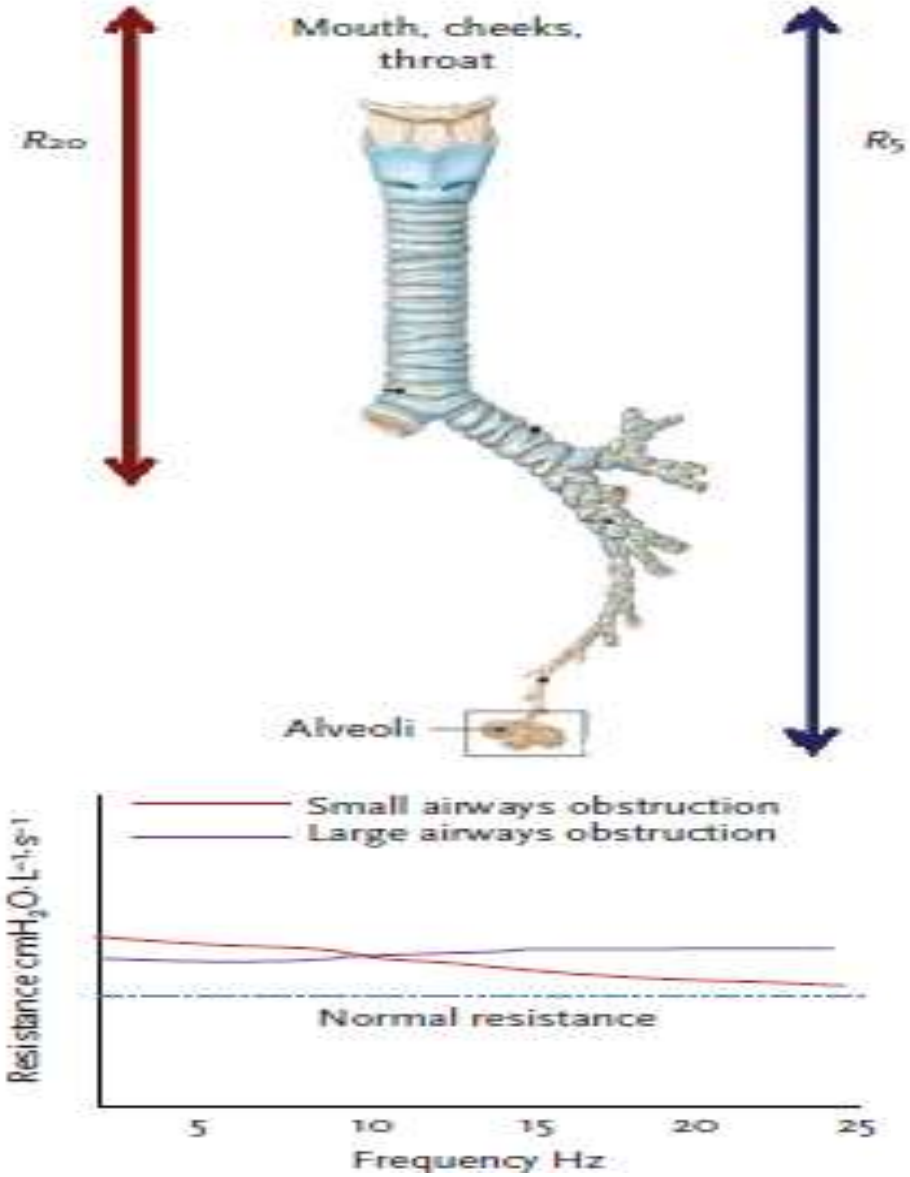
Salvi et al., ERS 2015

Forced Oscillation Technique / IOS

Large airway obstruction resistance is high at higher frequency

In small airway disease resistance is higher at low/ smaller frequency

Difference b/w two frequencies give information regarding small airway involvement



Salvi et al., ERS 2015

Physiological assessment of bronchiolar disorders – Forced Oscillation Technique / IOS

- Evidence largely restricted to smaller observational studies

- In a study of 32 asthmatic subjects CT imaging data was used to estimate resistance and its comparison with resistance measured by FOT showed good correlation

Berge et al . , Am J Respir Crit Care Med 2019

Physiological assessment of bronchiolar disorders
Forced Oscillation Technique/IOS

- Reactance indicates inertial and elastic properties of lung
- Difference b/w inspiratory and expiratory reactance at lower frequencies can help in detecting expiratory flow limitation(EFL) (Δ X5)
- EFL leading to air trapping is a common feature in small airway involvement

Dellaca et al ., ERJ 2014

Clinical Application Of FOT/IOS in Small airway disease

Clinical Significance of Forced Oscillation Technique for Evaluation of Small Airway Disease in Interstitial Lung Diseases

Masashi Mikamo[1] · Tomoyuki Fujisawa[1] · Yoshiyuki Oyama[1] · Masato Kono[1] · Noriyuki Enomoto[1] · Yutaro Nakamura[1] · Naoki Inui[2] · Hiromitsu Sumikawa[3] · Takeshi Johkoh[4] · Takafumi Suda[1]

ABSTRACT

Purpose Small airway disease (SAWD) in patients with interstitial lung disease (ILD) is often assessed by high-resolution computed tomography (HRCT). However, frequent HRCT examinations result in a high level of radiographic exposure. This study investigated the utility of the forced oscillation technique (FOT) to evaluate SAWD in patients with ILD.

Methods Broadband FOT using a commercially available device (MostGraph-01) and pulmonary function tests (PFT) were performed in 90 patients with ILD. HRCT images taken within 3 months were reviewed. The patients were divided into two groups according to the presence or absence of SAWD findings detected by HRCT. Clinical characteristics, PFT, and FOT between the two groups were compared.

Results Of the 90 patients with ILD, 19 were classified as having SAWD findings (the presence group) and 71 as not having SAWD findings (the absence group). There were no significant differences in parameters of PFT between the groups. The presence group had significantly lower values of reactance at 5 Hz (X5), resonant frequency (Fres), and low-frequency reactance area (ALX) than did the absence group. A within-breath change analysis demonstrated that the change in X5, Fres, and ALX between expiration and inspiration (ΔX5, ΔFres, ΔALX, respectively) was significantly different between the groups. A univariate analysis revealed that X5, Fres, ALX, ΔX5, ΔFres, ΔALX were significantly associated with the presence of SAWD findings. Multivariate analysis validated that Fres was related to the presence of SAWD findings.

Conclusions The FOT may be useful in detecting and evaluating SAWD in patients with ILD. Trial registration: UMIN 000020733.

Keywords Interstitial lung disease · Small airway disease · Forced oscillation technique · Reactance

Abbreviations

ALX	A low-frequency reactance area
AUC	Area under the curve

FOT parameters differed in ILD patients with Small airway involvement diagnosed with HRCT

Mikamo et al ., Lung 2016

Exhaled Nitric Oxide

- NO is produced by resident epithelial cells and inflammatory cells
- Measured during tidal exhalation
- FeNO exhibits flow rate dependency, at low flow FeNO reflects contribution of central airways and at higher flow represent alveolar contribution
- Raised alveolar FeNO is found to correlate with other measures of small airway dysfunction(in asthmatics) [2]

FeNO has largely been evaluated in asthma
Role in other small airway diseases is not known

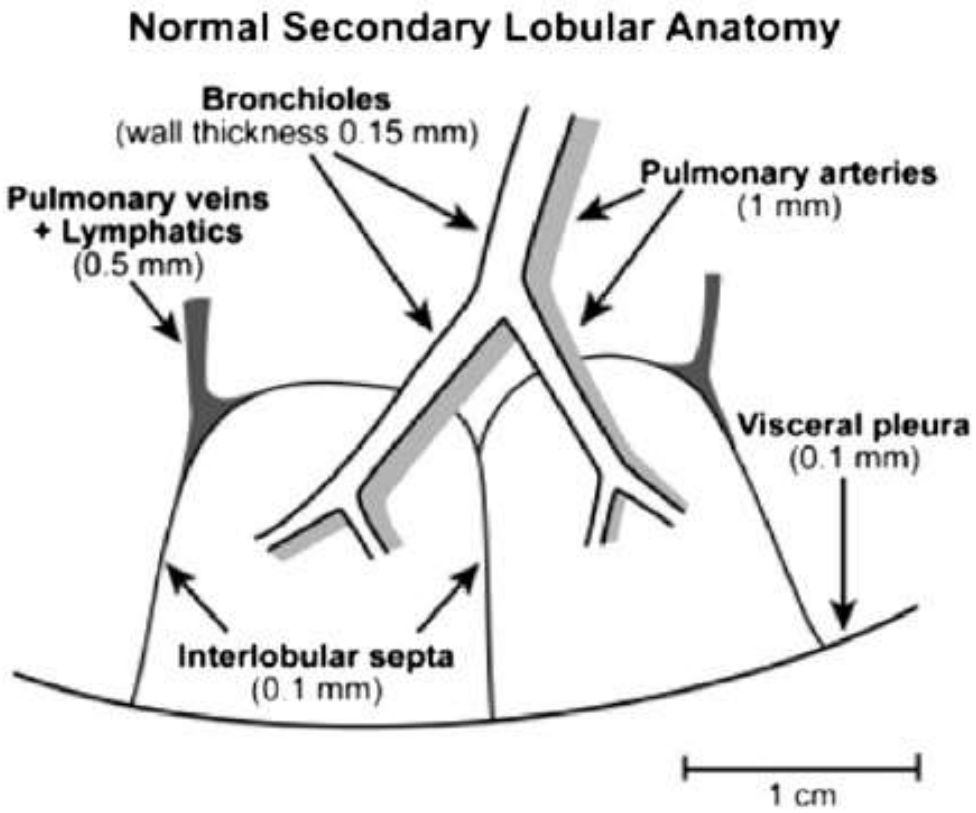
1 Mcnulty et al., EUR Clin Respir J. 2014
2 Veen et al., ERJ 2006

Physiological Assessment of bronchiolar disorders challenges

- Most of the available tests are not specific for small airway involvement
- Due to their vast number, significant amount of small airways must be affected for detecting a abnormality in the tests
- Evidence limited to mostly asthma, COPD
- Lack of reference values for newer tests

Stockley et al., Int J Chron Obstruct Pulmon Dis. 2017

Radiological features of bronchiolar disorders



Any alteration in three components of secondary pulmonary lobule

- Centrilobular structure
- Lobular parenchyma
- Interlobular septa

Lead to abnormalities being detected on HRCT

Bronchioles are component of centrilobular structure

Devakonda et al., CHEST 2010

Radiological features of bronchiolar disorders

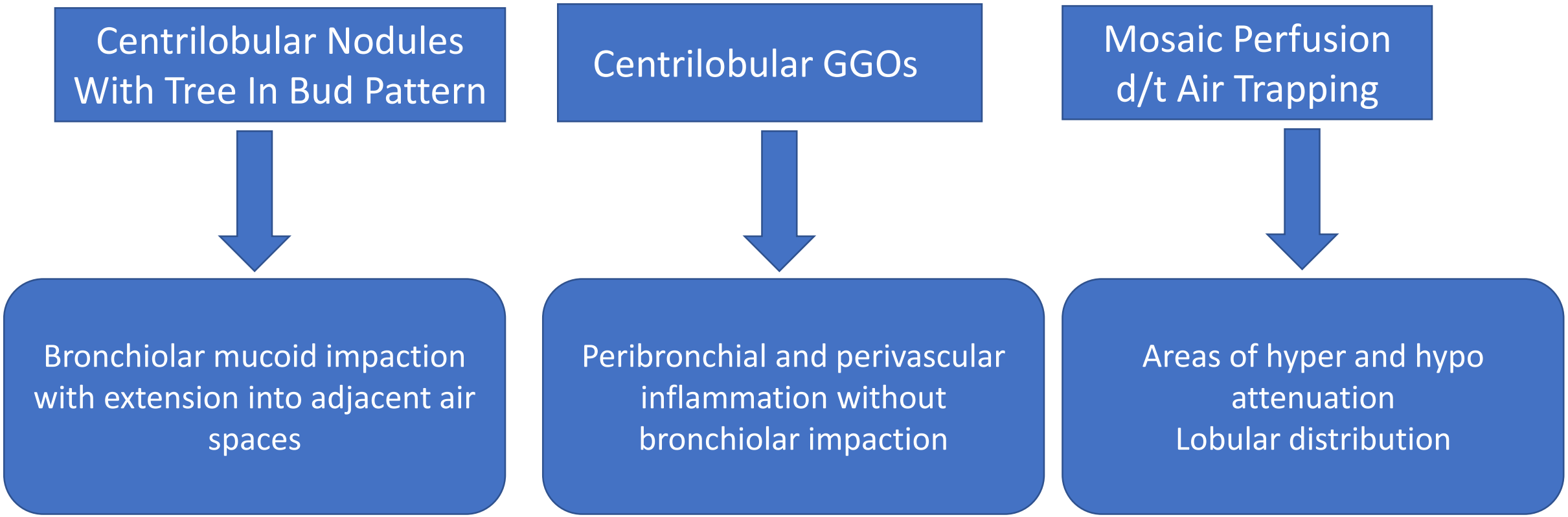
- Normal bronchioles are outside the resolution of HRCT chest
- However when diseased, bronchioles can be identified by direct and indirect signs
- HRCT chest with inspiratory and expiratory cuts is required for assessment of small airway disorders

Radiological signs in bronchiolar diseases

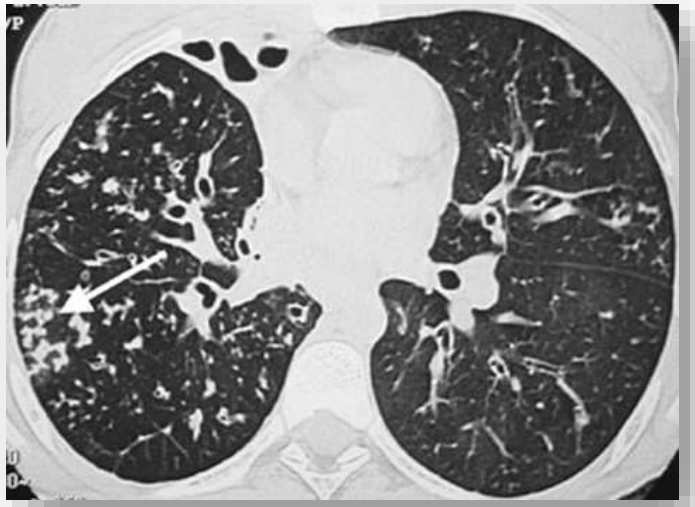
Direct Signs	Indirect signs
Bronchiolectasis	Mosaic perfusion
Bronchiole wall thickening	Sub segmental atelectasis
Centrilobular Nodules + TIB (inspissation of secretions)	
Centrilobular GGOs (peribronchiolar and perivascular inflammation)	

Devakonda et al., CHEST 2010

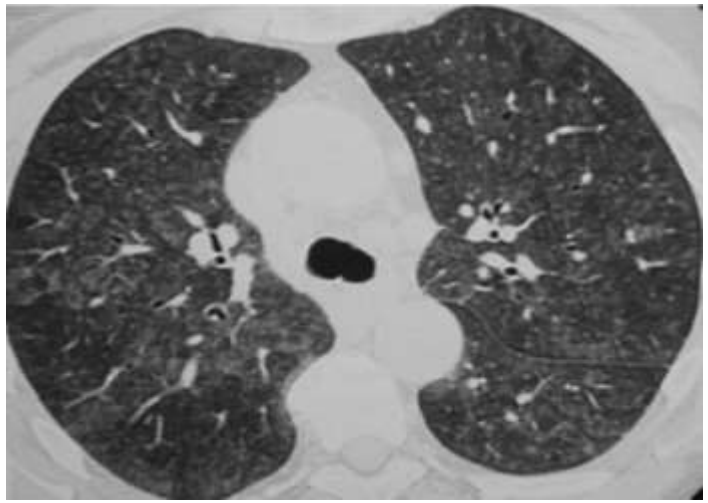
Radiological Patterns in bronchiolar diseases



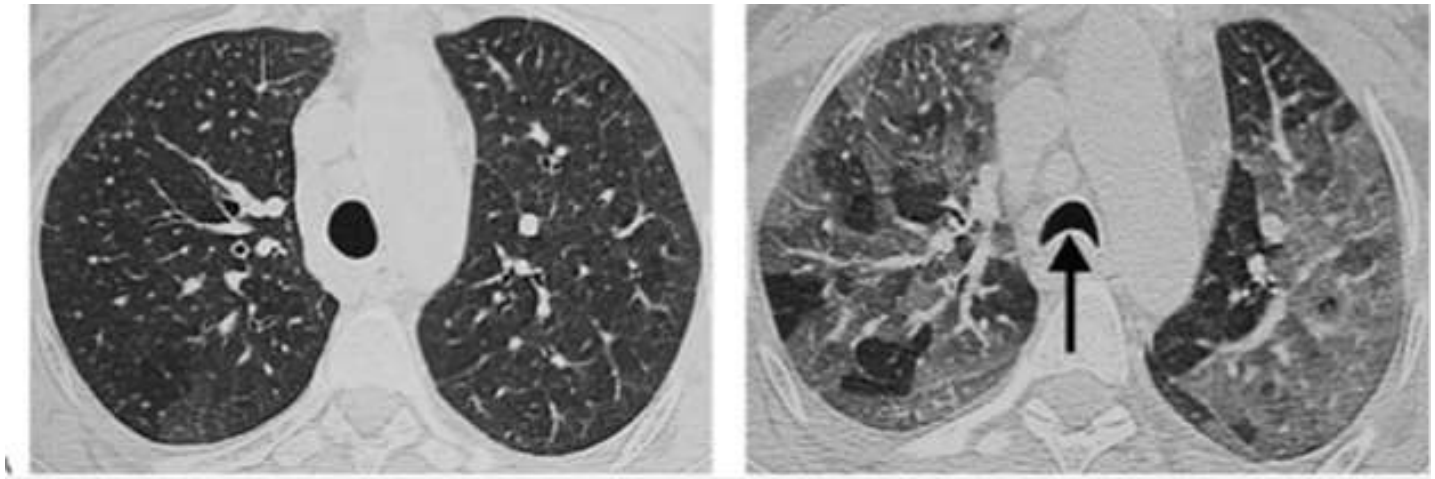
Radiological Patterns in bronchiolar diseases



CLN + TIB



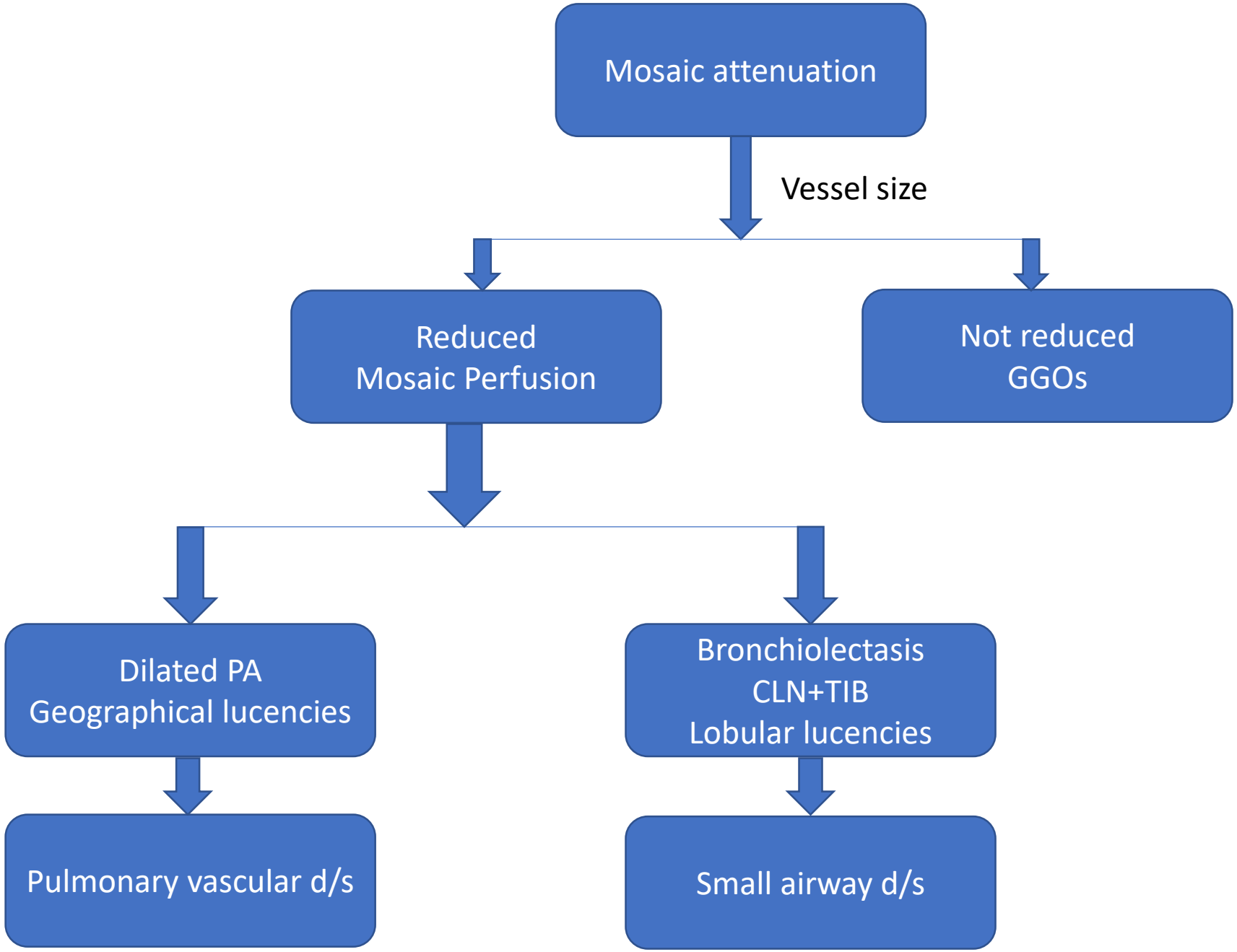
CL GGOs



MOSAIC PERFUSION - AIR TRAPPING

Differential diagnosis based on radiological pattern

CLN + TIB	CL GGOs	Mosaic perfusion
Focal : Infectious bronchiolitis UL : M Tb ML : NTM	UL : RB/RBILD	HP Constrictive bronchiolitis
Diffuse : ABPA Diffuse pan bronchiolitis Diffuse aspiration bronchiolitis CF,PCD	HP Follicular bronchiolitis Mineral dust airway d/s	


Mosaic attenuation
Vessel size
Reduced
Mosaic Perfusion
Not reduced
GGOs
Dilated PA
Geographical lucencies
Bronchiolectasis
CLN+TIB
Lobular lucencies
Pulmonary vascular d/s
Small airway d/s

Radiological signs in bronchiolar diseases

- Features of primary airway or parenchymal involvement may be seen on HRCT

  Bronchiectasis, emphysema, consolidation etc.

Devakonda et al., CHEST 2010

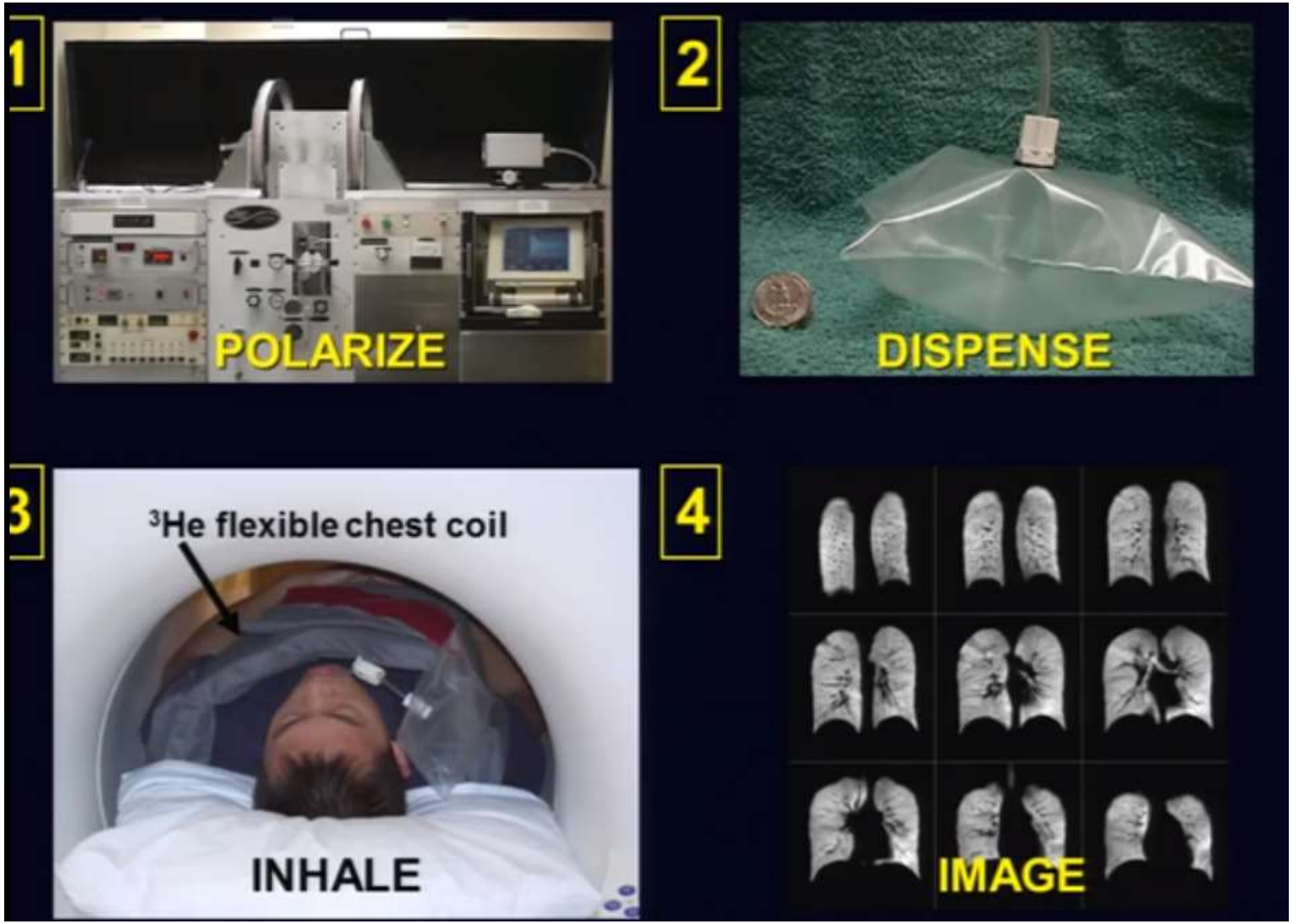
Radiological Assessment Of Small Airways
Hyperpolarized Gas (^{3}He and ^{129}Xe) MRI

- Conventional proton based MRI is not useful in routine lung imaging
- Suffers from drawbacks d/t low proton density and motion artefacts resulting in low resolution
- Hyperpolarization(alignment of nuclear spins) helps overcome these drawbacks
- Hyperpolarized noble gases act as external gaseous contrast media which help in imaging airways and distal airspaces

Kern et al ., Br J Radiology 2018

W Mcnulty et al., Eur Clin Respir J 2014

Hyperpolarized Gas MRI protocol



Gives information on

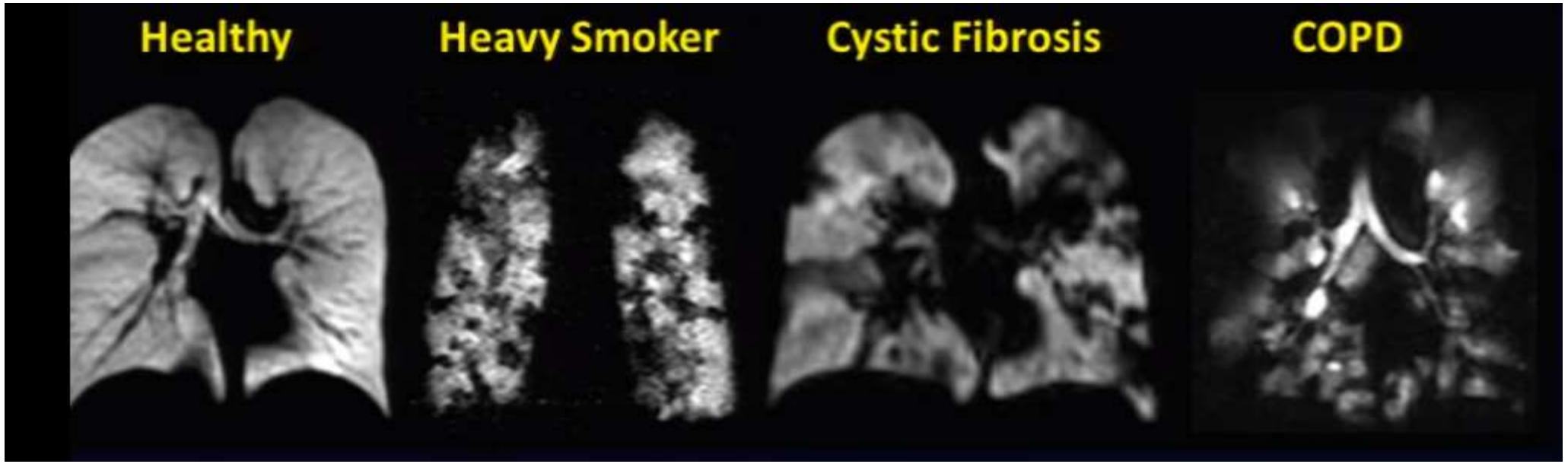
1. Ventilation
2. Microstructure of lungs

Kern et al ., Br J Radiology 2018

Hyperpolarised Gas MRI – Distribution of ventilation

- Static Imaging : Look for distribution of gas following deep inhalation

  Defects in distribution indicate ventilation heterogeneity



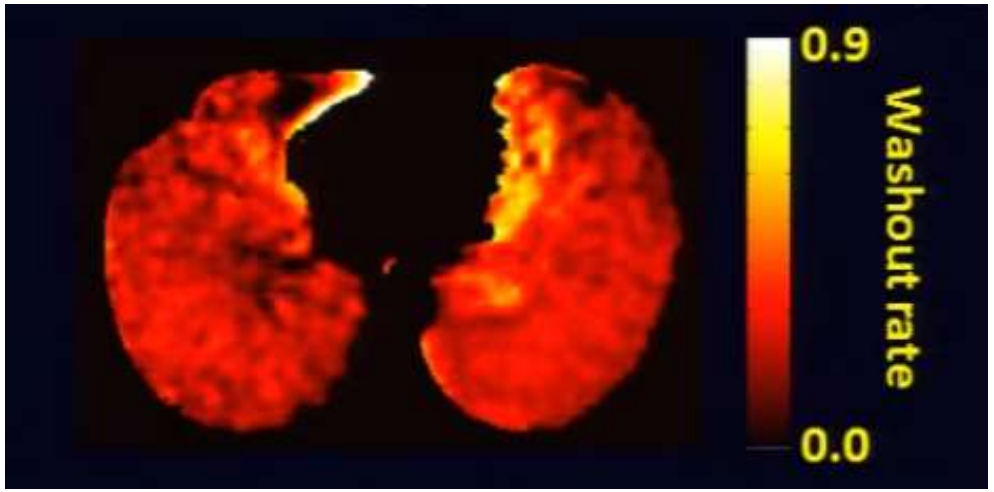
Kern et al ., Br J Radiology 2018

Hyperpolarised Gas MRI – Distribution of ventilation

- Dynamic imaging –

  Repeated acquisition following gas administration

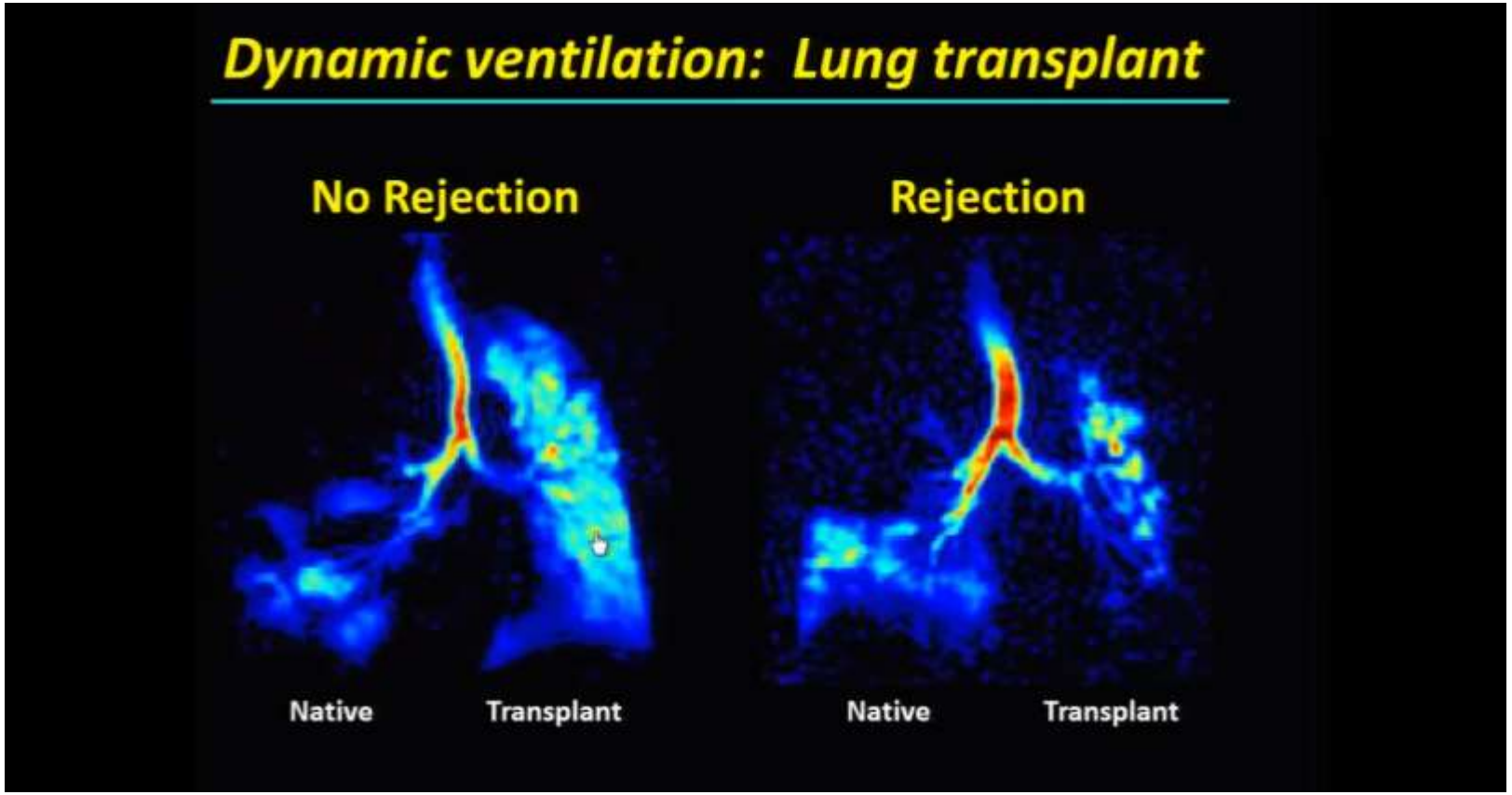
  Gives information on ventilation, areas of gas trapping, gas washout rate



Areas of differential He clearance have been seen to correlate with air trapping seen on CT

Deppe et al ., ISMRM 2011

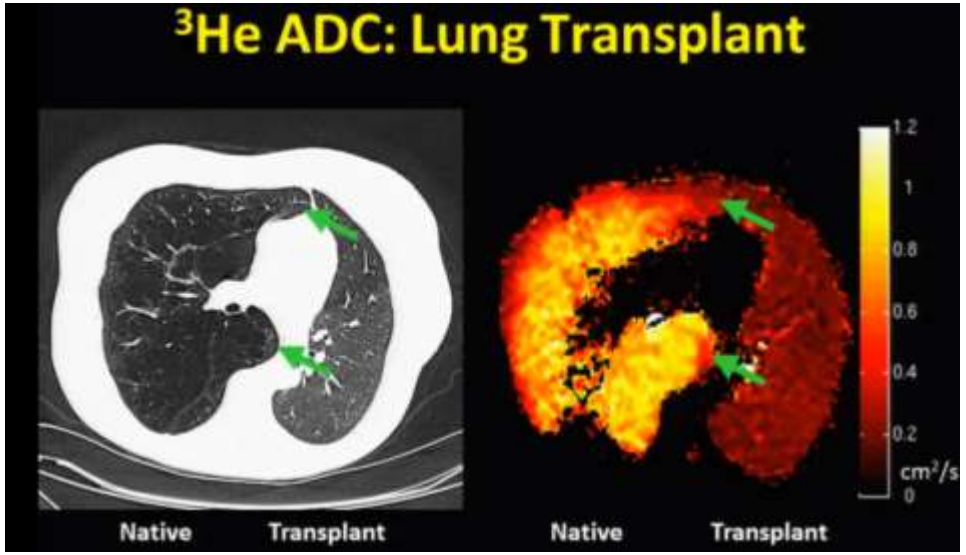
Hyperpolarised Gas MRI – Distribution of ventilation
Clinical application – Post Lung Transplant



Salerno et al ., RSNA 20O1

Hyperpolarized Gas MRI – other sequences

- Apparent diffusion co efficient(ADC) gives information on status of distal airspaces



Higher ADC values correspond to tissue destruction

Nuclear medicine techniques
Gamma scintigraphy

- Gamma ray emitting radio nuclides are used to image the lung as they decay
- Distribution of radio nuclides gives information regarding ventilation
- Being a 2 dimensional technique exact localization is difficult

W Mcnulty et al., Eur Clin Respir J 2014

SPECT

- 3-d imaging modality for assessment of regional lung ventilation
- SPECT can be used to image ventilation using either radiolabelled gases or ultrafine particles (Technegas)
- Technegas is Technetium labelled ultrafine carbon particle which has high peripheral deposition
- It impacts and does not move peripherally if there is narrowing of airways
- This heterogeneity in its deposition can be picked up with SPECT

Gregory King, Respiration 2012

SPECT

- Ventilation heterogeneity in a asthmatic patient post methacholine challenge

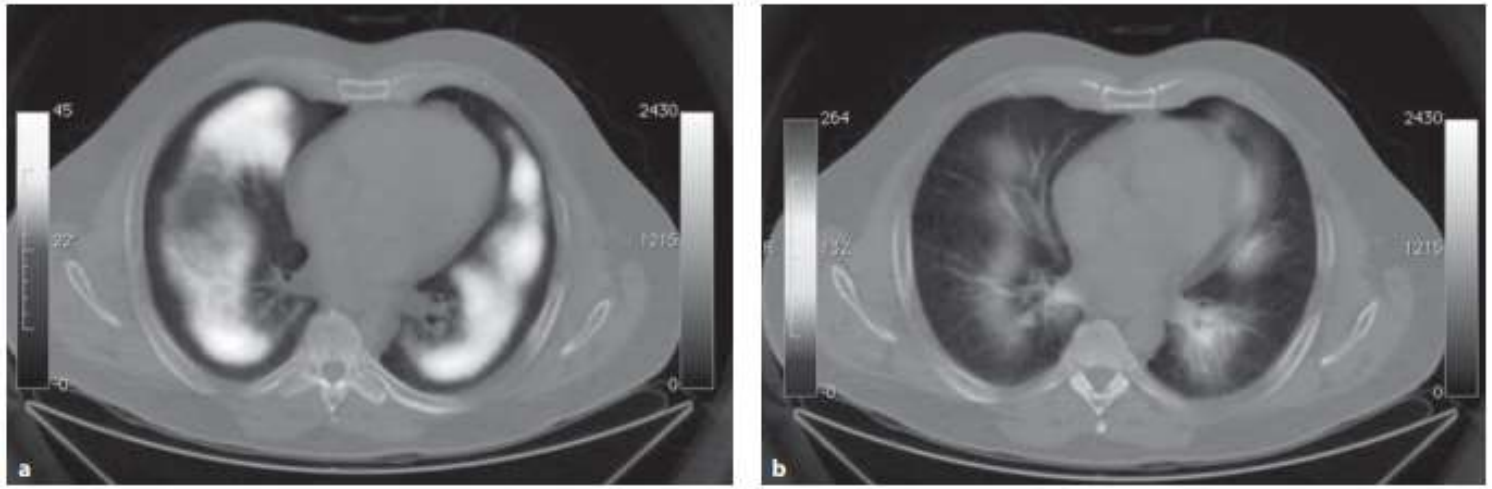


Fig. 2. a SPECT/CT fusion Technegas imaging of an asthmatic patient at baseline. Ventilation is mildly heterogeneous. The lack of apparent ventilation to the lung periphery is likely due to insufficient resolution to detect low ventilation. **b** Ventilation imaging post-methacholine challenge when FEV_1 was reduced by approximately 20%. Note the reduction in ventilated volume and more heterogeneous distribution, which is based on small airway function.

Gregory King, Respiration 2012

SPECT

- V/Q SPECT has been used in COPD patients to assess ventilation heterogeneity

PET

- Regional distribution of ventilation and perfusion can be assessed using radioisotopes

- In smaller studies Krypton, Technetium labelled albumin and NN_{13} have been used to assess ventilation and perfusion defects in asthma patients

- Using modelling techniques site of ventilation defect can be deduced proximal/ distal airway

Gregory King, Respiration 2012

Assessment techniques for small airway

	Measures	Pros	Disadvantages
Spirometry	FEV1, FEF 25-75%	Simple to perform Reproducible	Insensitive to early change Effort dependent
FOT/IOS	R5-R20 Δ X5	Non invasive Effort independent	Equipment availability Reference values not available
Inert gas washout	Closing capacity and volume Phase III slope, Sacin, Scond	Sensitive to early changes	Difficult to perform Specialized equipment
FENO	Exhaled nitric oxide	Easy and quick to perform	Affected by smoking
HRCT	Direct and indirect signs	Widely available Quick and easy to perform	Unable to visualize small airways directly
Nuclear medicine techniques(PET, SPECT)	Ventilation V/Q	Ventilation heterogeneity V/Q	Expensive Radiation Exact anatomic localization X
Hyperpolarised MRI	Static ventilation Dynamic ventilation Apparent Diffusion Coefficient	Ventilation heterogeneity Lung microstructure No radiation dose	Expensive Research application Availability

Bronchiolar diseases : Role of lung biopsy

- Conditions in which clinical details radiological findings sufficient for diagnosis : Subacute HP
- Bronchoalveolar lavage in infectious etiology
- TBLB in post transplant bronchiolitis (at least 5 sample)
- SLB in rest of the conditions

Bronchiolar diseases : Role of Cryo biopsy

OPEN

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

Syakirin Sirol Aflah Syazatul[1,2,7], Sara Piciucchi[3,7✉], Sara Tomassetti[4], Claudia Ravaglia[1], Alessandra Dubini[5] & Venerino Poletti[1,6]

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.

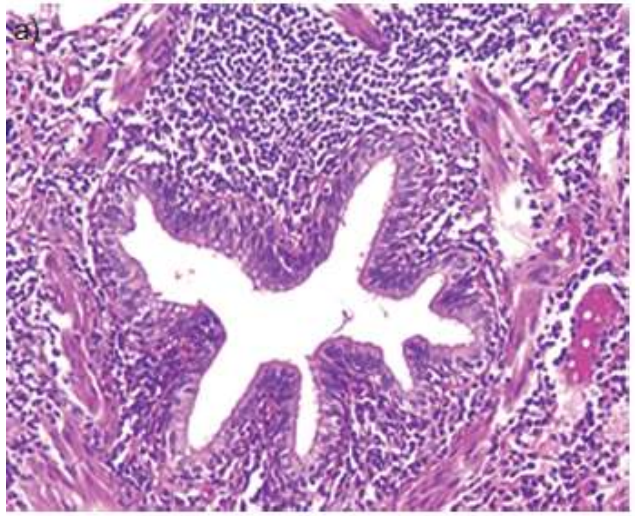
Retrospective study of 23 patients

Diagnosis achieved through MDT

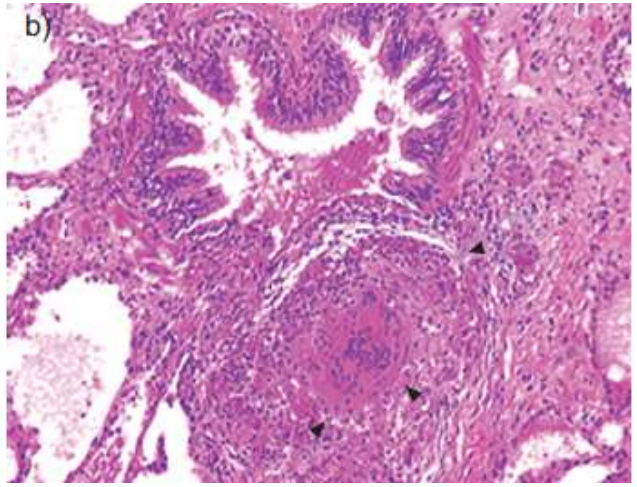
Complications in 2 patients in form pneumothorax

Syazatul et al ., Sci Rep. 2020

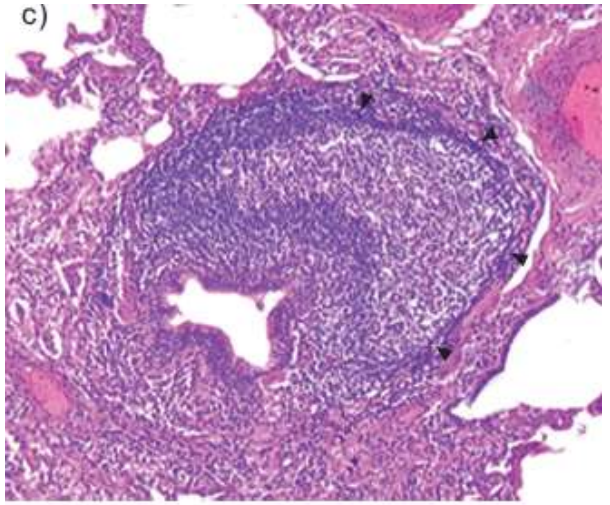
Histopathological patterns in bronchiolitis



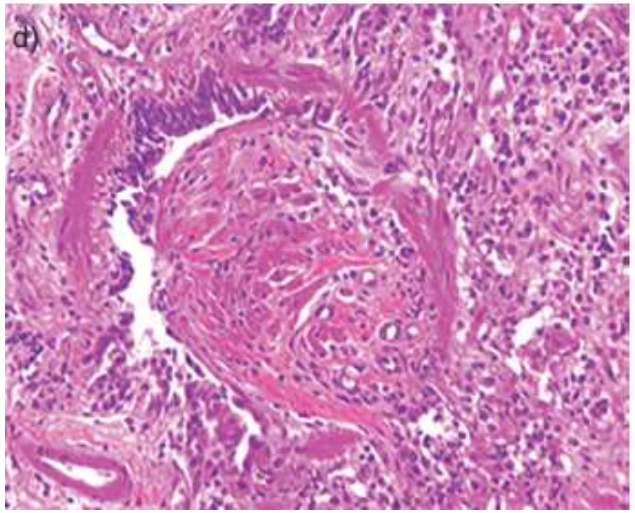
CELLULAR BRONCHIOLITIS



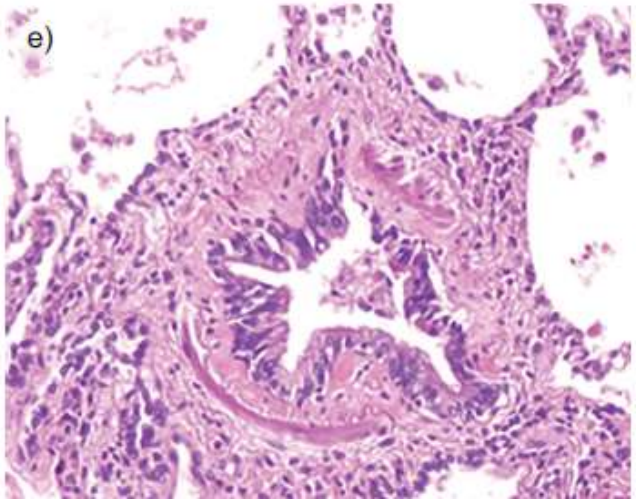
GRANULOMATOUS BRONCHIOLITIS



FOLLICULAR BRONCHIOLITIS



PROLIFERATIVE BRONCHIOLITIS



CONSTRICTIVE BRONCHIOLITIS

Individual disorders

Proliferative Bronchiolitis

Condition	Aetiology	Clinical Feature	PFT and Radiology	Histopathology	Treatment
Pathological pattern of intrabronchiolar polyps composed of myofibroblastic tissue that occlude the lumen from within	-Cryptogenic -Secondary to variety of insults • Post infection • Toxins • CTD • Aspiration • Post obstruction	Subacute dyspnoea and cough	Restrictive pattern ↓ DLCO Mosaic perfusion Peripheral patchy pleural based consolidation(if alveolar involvt +)	Intrabronchiolar polyps composed of granulation tissue which may extend into alveolar spaces	Glucocorticoids

C Ravaglia et al.,Semin Respir Crit Care Med 2020

Constrictive Bronchiolitis

Condition	Aetiology	Clinical Feature	PFT and Radiology	Histopathology	Treatment
Narrowing of bronchiolar lumen due to extrinsic compression by fibroinflammatory process	• Chronic rejection post lung transplant • Chronic GVHD post allogenic HSCT • Acute/chronic chemical exposure • CTD • Post Infective	Progressive dyspnoea and cough	Obstructive pattern (w/o BDR) Mosaic perfusion	Cellular infiltrates in bronchiolar wall Bronchiolar smooth m/s hypertrophy Obliteration/narrowing of bronchiolar lumen	Treatment of underlying cause

C Ravaglia et al.,Semin Respir Crit Care Med 2020

Constrictive Bronchiolitis - Aetiology

Inhalational injury
Irritant gases(chlorine, ammonia)
Toxic fumes(nitrogen oxides)
Mineral dust
Volatile flavouring agents(diacetyl)
Vaping

Post Infectious
Virus(RSV, adenovirus, influenza)
Bacterial(Mycoplasma, Bordetella)

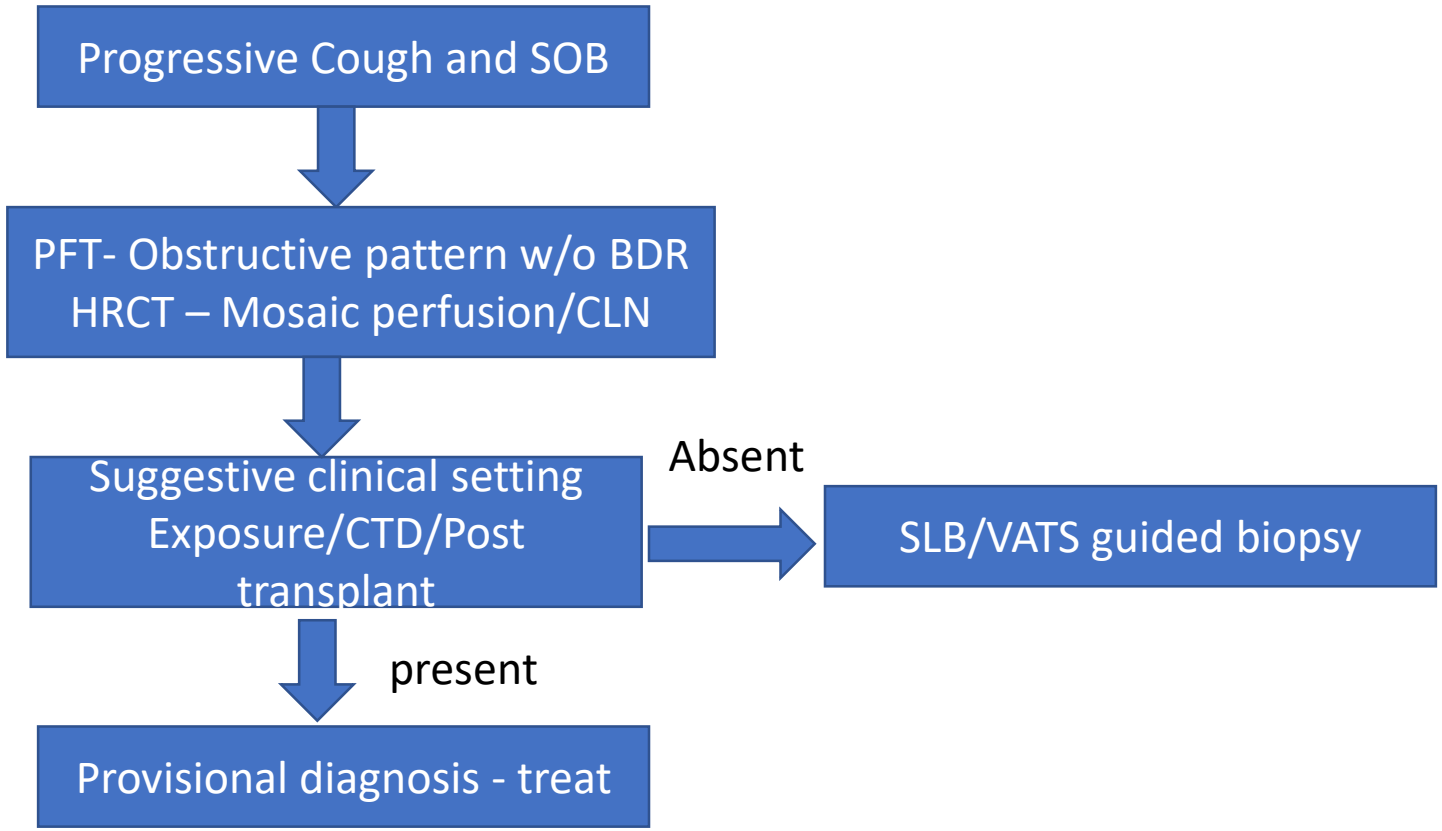
Drug induced
Penicillamine
Gold
Busulfan, Sulfasalazine
Nimesulide, Rituximab

Post Transplant
Bone marrow
Lung
Heart-Lung

Idiopathic
Cryptogenic
CTD associated
Paraneoplastic pemphigus
Diffuse idiopathic NE cell hyperplasia

Swaminathan et al ., ATS Annals 2019

Constrictive Bronchiolitis - Diagnosis



Constrictive Bronchiolitis – Treatment(Non transplant)

Modality	Drug	Evidence
Symptom based and Supportive treatment	Inhaled bronchodilator Cough suppressants Vaccination and rehabilitation	-
Cessation of culprit drugs and exposure	-	-
Macrolide antibiotics	Erythromycin 400-600mg/d for 6 months Azithromycin 250 mg/d for 6 months	Small case series show stabilization in lung function [1]
Corticosteroids	Glucocorticoids	Case series show no benefit in non rheumatic disease associated constrictive bronchiolitis [1,2]
Other immunosuppressants	Methotrexate/Cyclophosphamide /Etanercept	Not shown to be associated with improvement in lung function [1,2]

1Callahan et al ., Mayo clinic proc. 2019
2 Parambil et al . , Respirology 2009

Constrictive Bronchiolitis – Post Transplant

Bronchiolitis obliterans v/s Bronchiolitis obliterans syndrome

The International Society for Heart and Lung Transplantation (ISHLT) has proposed the term bronchiolitis obliterans syndrome (BOS) for patients with clinical manifestations compatible with bronchiolitis obliterans but without histopathological confirmation

A ≥20% drop in forced expiratory volume in the first second (FEV_1) from a stable post -transplant baseline, persistent over ≥3 weeks and not explained by other reversible pathologies

Burgel et al ., Eur Respir Rev 2013

Constrictive Bronchiolitis – Post Transplant

Parameter	Constrictive bronchiolitis post lung transplant	Constrictive bronchiolitis post allogenic HSCT
Risk factors		
Immunology	HLA mismatch	GVH disease
CMV Infection	Yes	Not established
Community acquired viral infections	Suspected	Suspected
GERD	Yes	Not established
Prevalence	9% at 1 year 38% at 5 year 58% at 10 year	5.5% - 14%

Constrictive Bronchiolitis Treatment(Transplant related)

Aetiology	Treatment
Post HSCT	Inhaled LABA+ICS(High dose) [2] Treatment of underlying GVHD [1] FAM therapy (Fluticasone/Azithromycin/Montelukast) [3] Prophylactic azithromycin not to be used post HSCT [4]

1.Burgel et al . , Eur Respir Rev 2013
2.Bergeron et al . , Am J Respir Crit Care Med. 2015
3.Norman et al ., Bone Marrow Transplant. 2011 Oct
4.Bergeron et al . , JAMA 2017

Constrictive Bronchiolitis Treatment(Transplant related)

Aetiology	Treatment
Post Lung Transplant	Azithromycin prophylaxis [1] Long term azithromycin treatment (250mg x 5d f/b 250mg thrice a wk) [2] Adjustment of maintenance immunosuppression (Tac/ MMF based) [3] Montelukast / Sirolimus/ Everolimus (salvage therapies)

1.Vos R et al . , Eur Respir Journal 2011
2.Corris PA et al . , Thorax. 2015
3.Hayes D et al ., J Cardiothorac Surg. 2011

Follicular Bronchiolitis

Condition	Aetiology	Clinical Feature	PFT and Radiology	Histopathology	Treatment
Pathological pattern of hyperplastic lymphoid follicle along wall of bronchiole	• CTD • Immunodeficiency synd. • Primary	Progressive cough and dyspnoea Recurrent pneumonia	Nonspecific PFT Centrilobular nodules with ill defined GGOs (cotton in bud app)	Hyperplastic lymphoid follicle along wall of bronchiole that encroach or obliterate lumen Sparing of interlobular septum	Treat underlying cause

Tashtoush et al ., J Clin Diagn Res 2015

Follicular Bronchiolitis

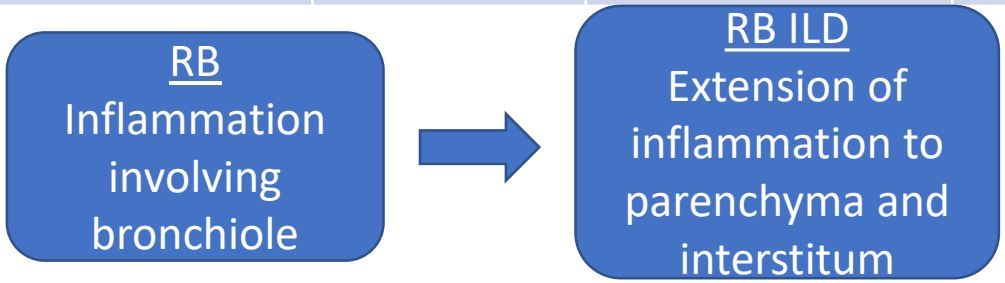
Clinico-pathological subtypes of Follicular Bronchiolitis

Groups		Features	Treatment
1	CTD related – RA and Sjogren's synd.	Features of CTD/Prog. SOB/cough	Immunosuppression
2	Immunodeficiency associated – HIV and CVID	Recurrent pneumonia/Prog. SOB	ART/IVIg
3	Primary/Idiopathic	SOB/cough	Steroids/macrolides *

Tashtoush et al ., J Clin Diagn Res 2015
* Case reports

Respiratory Bronchiolitis

Condition	Aetiology	Clinical Feature	PFT and Radiology	Histopathology	Treatment
Common form of bronchiolitis caused by smoking	Smoking	Asymptomatic Cough and dyspnoea if associated with RBILD	UL predominant Ill defined CL GGOs	Pigmented macrophages within lumen of respiratory bronchioles with varying degrees of chronic inflammation, peribronchiolar fibrosis and intraluminal mucostasis	Smoking cessation



C Ravaglia et al.,Semin Respir Crit Care Med 2020

Diffuse Pan bronchiolitis

Condition	Aetiology	Clinical Feature	PFT and Radiology	Histopathology	Treatment
Rare syndrome characterised by bronchiolar inflammation and chronic sinusitis	Japanese middle aged adults Non smoker ?Ass with HLA haplotypes(B54 and A11) ?Polymorphism in MUC 5B	Cough expectoration(>50ml/d), dyspnoea and sinusitis(75%)	Obstruction CLN+TIB	Lymphoplasmacytic inflammation with foamy macrophages involving wall of resp. bronchiole	Erythromycin 400-600mg/d for 6 months

Ryu et al., Am J Respir Crit Care Med, 2003

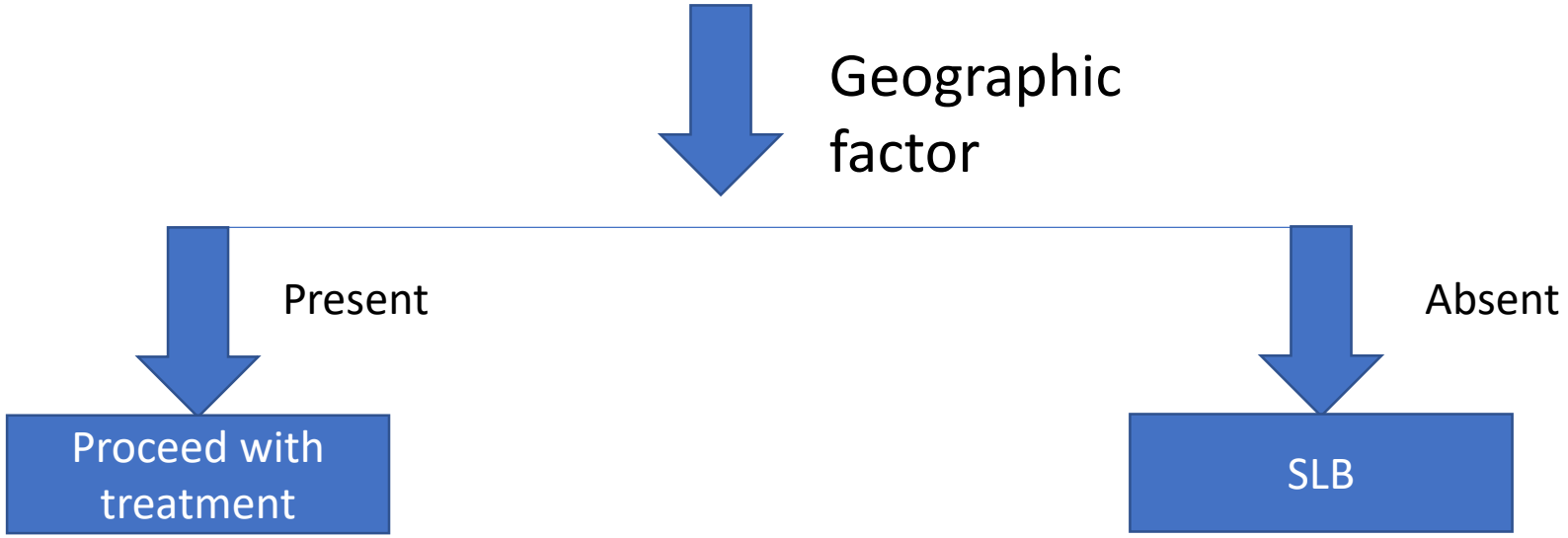
Diffuse Pan bronchiolitis

Diagnosis

ALL 3
Chronic sinusitis
Persistent cough, sputum , dyspnoea
B/L diffuse CLN

Plus

ANY 2
Coarse crackles
Cold agglutinins titre >64
FEV1<70% and PaO2 <80mmHg



Ryu et al., Am J Respir Crit Care Med, 2003

Diffuse Pan Bronchiolitis - Treatment

Cochrane Library

Cochrane Database of Systematic Reviews

Macrolides for diffuse panbronchiolitis (Review)

Lin X, Lu J, Yang M, Dong BR, Wu HM

Retrospective studies, Non RCTs and a single RCT show improvement in symptoms, survival and radiology with low dose macrolide therapy for at least 6 months

Erythromycin 400-600mg/d for at least 6 months 1st choice
Azithromycin and clarithromycin Alternatives
Rhinosinusitis and superadded infections to be addressed

Lin et al ., Cochrane Database Syst Rev. 2015

Acute Bronchiolitis

Condition	Aetiology	Clinical Feature	PFT and Radiology	Histopathology	Treatment
Common in infants and children Uncommon in adults	Infection – viral and non viral Non infectious- Aspiration /toxic inhalation	dyspnoea, wheeze and cough	Restrictive pattern ↓ DLCO CLN + TIB (focal)	Neutrophil infiltrate in bronchiole wall	Supportive care

C Ravaglia et al.,Semin Respir Crit Care Med 2020

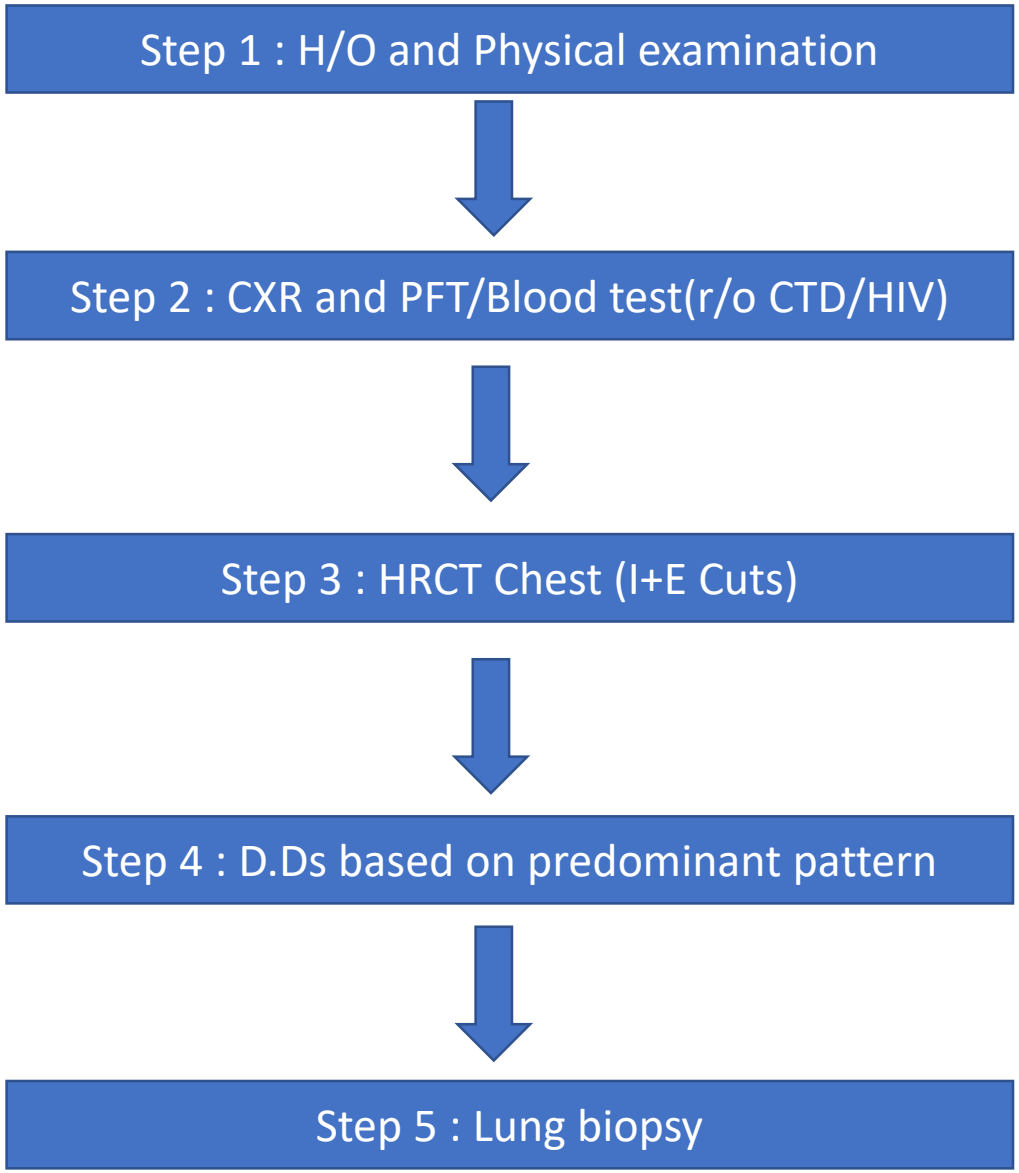
Diffuse Aspiration Bronchiolitis

Condition	Aetiology	Clinical Feature	PFT and Radiology	Histopathology	Treatment
Chronic inflammation of bronchioles caused by recurrent aspiration	Recurrent Aspiration d/t GERD Drug abuse Dysphagia	Recurrent episodes of dyspnoea, cough, sputum production and fever	LL predominant CLN + TIB	Chronic inflammation with foreign body giant cells in bronchioles	Prevention of recurrent aspiration

Risk factor, Recurrent pneumonia, consistent Radiology

Hu et al ., J Bras Pneumol. 2015

Algorithm



CTD/Drug/
Exposure/Infection
/Transplant

Normal/
Non specific

CLN + TIB
CL GGOs
Mosaic perfusion

In most
cases

Conclusion

- Small airway disorders include entities with diverse aetiology, radiological and histological features
- Disproportionate symptoms, normal conventional PFTs and findings on radiology can be initial clue to these disorders
- Multi disciplinary approach in a step wise manner is required to reach a diagnosis
- Emerging diagnostic tests may help in better understanding and identification of these disorders