

Uncommon PFTs: Multiple  
breath washouts and Forced  
oscillation techniques

Multiple breath washouts

# Background

- Most chronic lung disease Asthma COPD Bronchiectasis Cystic fibrosis – heterogenous distribution
- Small airways constitute 70-80% of the total lung volume
- Contribute little to airway resistance
- Conventional PFT (Spirometry) – little information about these small airways
- Ventilation distribution abnormalities despite normal ventilatory capacity by spirometry

# Background

- Ventilation distribution occurs by convection and diffusion
- Mechanisms of inhomogeneity
  - Convection-dependent inhomogeneity (CDI) in the conducting airway zone (i.e. airways proximal to terminal bronchioles)
  - Diffusion-limitation related inhomogeneity in pathologically enlarged acinar structures (rare)
  - Interaction between convection and diffusion in an intermediate zone at the level of the diffusion-convection front

# Background

- Gas mixing tests – MBW reflect small airway function
- By studying inhomogeneity in ventilation
- Normal – Inhomogeneity exists
  - Asymmetry of small airways and acini
  - Gravity
- Disease – further increase degree of normal inhomogeneity in ventilation
- Washout tests may provide insight into mechanisms behind abnormal ventilation distribution and localization of pathology

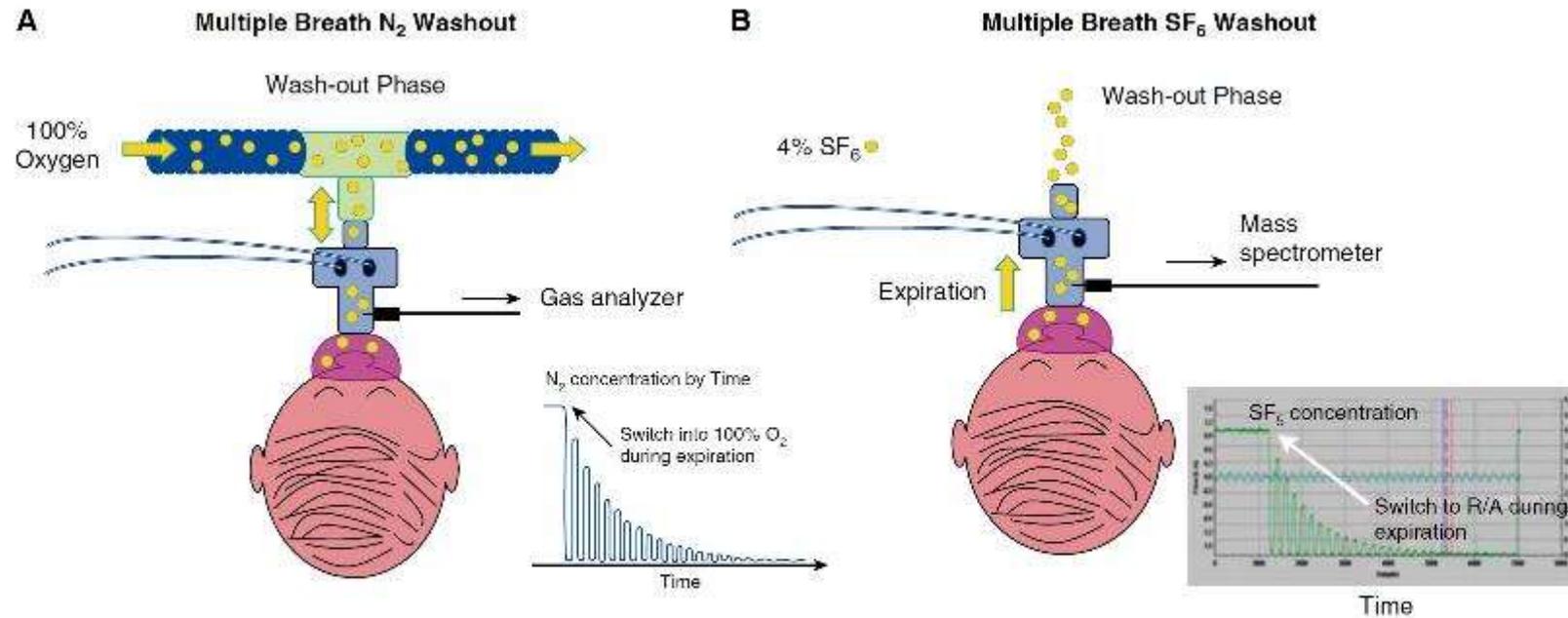
# Feasibility

- Requires only tidal breathing
- No forced manoeuvre required
- Useful in individuals unable to perform spirometry
- Pediatric population

# Procedure - MBW

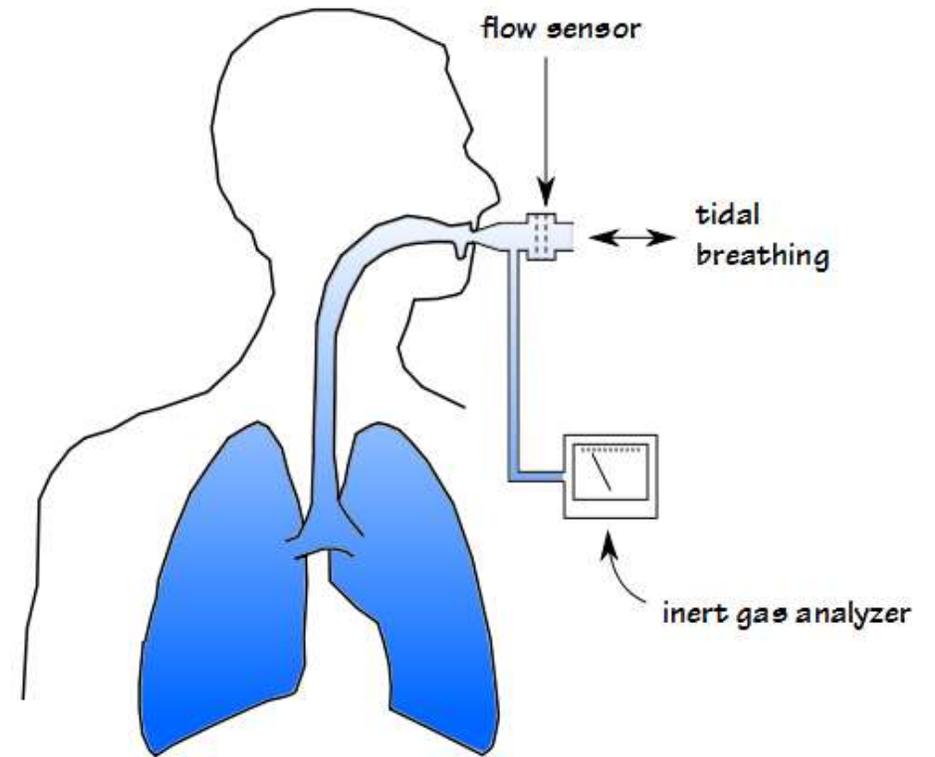
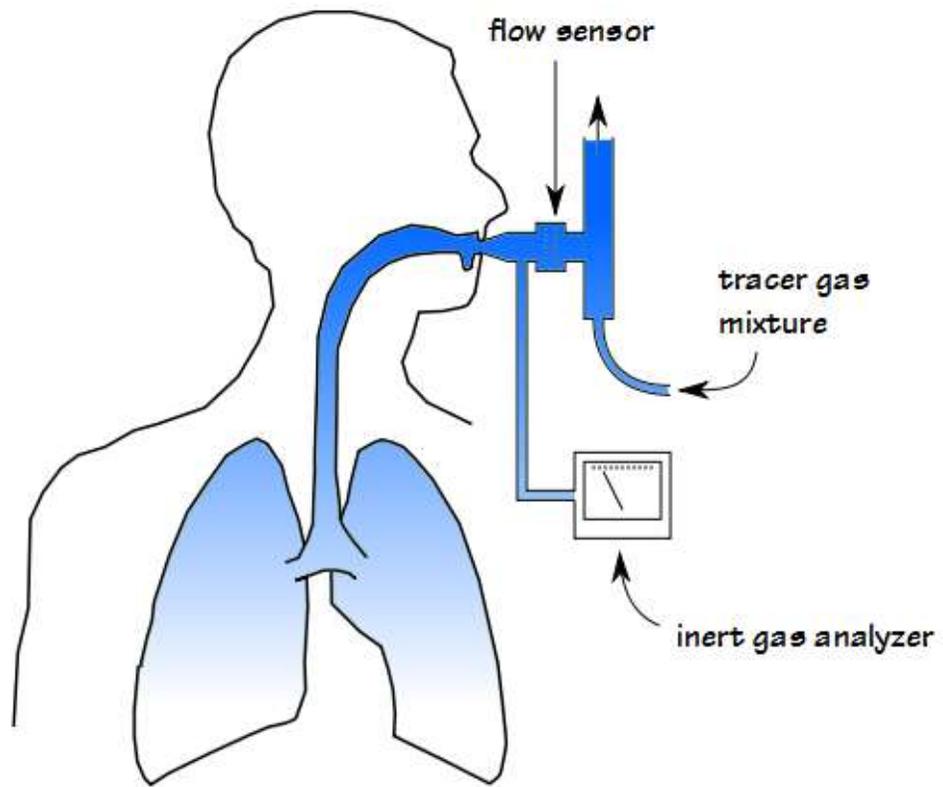
- Wash-in phase - test gas is delivered at a known concentration
- Wash-in complete - the expired gas concentration reaches the delivered gas concentration
- gas mixture is breathed until 30 or 60 seconds after concentrations have equalized (ERS/ATS statement says 5 minutes for adults and 4 minutes for children).
- Assessed by gas analyser
- N<sub>2</sub> – No wash in
- Wash-out phase – Room air or 100 O<sub>2</sub> inhaled – Normal tidal breaths
- End tidal concentration of inert gas is analysed
- Wash-out stopped once concentration falls to 1/40<sup>th</sup> the initial end-tidal concentration (2.5% of initial concentration)

# Procedure - MBW



**Figure 1.** Schematic representation of two washout phase tests using the two techniques. (A) N<sub>2</sub>-based setup. During the N<sub>2</sub> washout, 100% oxygen is delivered using a bias flow. The blue tracing shows the decay in the N<sub>2</sub> signal during expiration. (B) Extrinsic gas, SF<sub>6</sub>-based setup. The green tracing shows the decay in the SF<sub>6</sub> concentration during the washout-phase. R/A = room air.

# Procedure - MBW

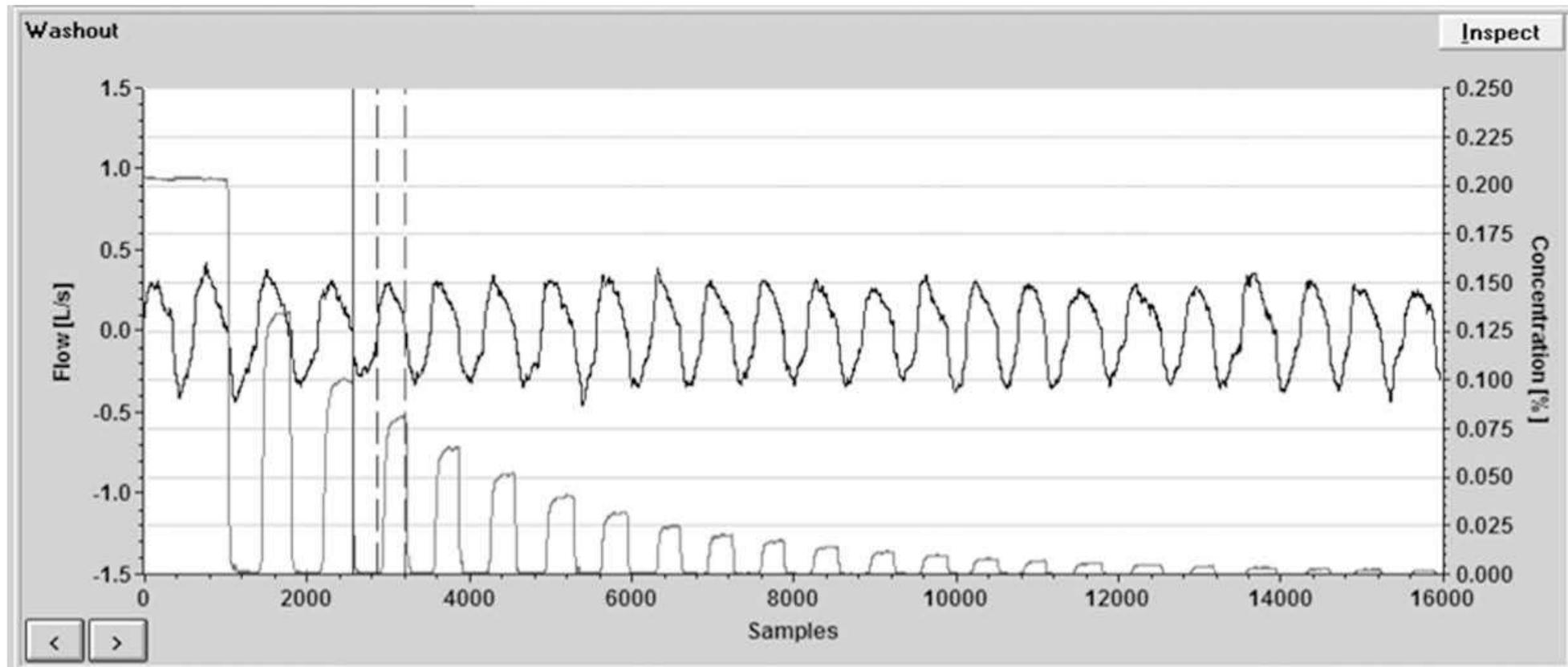


# Procedure - MBW



**Figure 2** Subject performing a washout. The supply of wash-in gas (0.2% SF<sub>6</sub> in air) is provided by the cylinder in the background. An Innocor™ gas analyser is used to measure flow and SF<sub>6</sub> concentration and expiratory volume is displayed to the subject on a separate screen.

# Procedure - MBW



# Principle

- Measures inert gas clearance over multiple tidal breaths as the patient breathes pure oxygen and washes out the ambient nitrogen in the lung
- the multiple-breath washout test can also be performed with inhalation (wash-in phase) and subsequent exhalation (wash-out phase) of inert gases such as helium or sulfur hexafluoride (SF<sub>6</sub>)
- Inert gas –
  - safe at concentrations used
  - not participate in gas exchange
  - not dissolve significantly in blood or other tissues. Options
- Other options – argon, helium and methane

# Lung clearance index (LCI)

- Airway obstruction gas distribution -more uneven and the mixing and turnover longer.
- The Lung Clearance Index (LCI) is measure of inhomogeneity
- a description of how much ventilation is required to completely clear the FRC.
- It was first described by Margaret Becklake in 1952
- Revived now because of advancement in gas analyzer, flow systems and software
- Defined as the number of FRC lung volume turnovers required to drive the nitrogen concentration down to one fortieth of the starting nitrogen concentration

# Lung clearance index (LCI)

- It is calculated as the number of lung volume turnovers required to clear the lung of the inert gas
- Lung volume turnovers reflect the FRC which is measured during the washout test.

$$FRC(L) = \frac{\text{Volume of inert gas (L)}}{F_{\text{trace}}_{\text{initial}} - F_{\text{trace}}_{\text{final}}}$$

$$LCI = \frac{\text{Cumulative Exhaled Volume (L)}}{FRC(L)}$$

- $F_{\text{trace}}$  = fractional concentration of tracer gas

# Lung clearance index (LCI)

- FRC tends to be lower when measured with SF6 than with N2
- This is likely due to the fact that SF6 must be washed-in before it is washed-out and it may not completely equilibrate with the poorly ventilated parts of the lung
- LCI tend to be higher with SF6

# Technical considerations

- The most widely used inert gases are N<sub>2</sub> and SF<sub>6</sub>. N<sub>2</sub> MBW requires only 100% oxygen (O<sub>2</sub>) during the washout phase, which is readily available but may not be appropriate for use in infants due to effects of pure oxygen on tidal breathing parameters

# Technical considerations

- N<sub>2</sub> diffusion to washout characteristics, although believed to be negligible in healthy individuals, has not been rigorously studied
- SF<sub>6</sub> MBW seems physiologically preferable for use across all ages, high cost and limited availability.
- Furthermore, SF<sub>6</sub> was listed in the Kyoto protocol as one of the top six gases whose release should be limited
- N<sub>2</sub> is becoming more widespread and is being used for all age groups except infants

# Technical considerations

- Measurements different inert gases are not interchangeable
- Normative data generated from one system should not be used for other devices
- validation of equipment in young children and normative data for all age groups are key priority areas

# Technical considerations

- Test duration
  - 2-5 mins of tidal breathing per manoeuvre
  - Longer time in airway obstruction
- Number of trials
  - criteria defining the “best attempt” are difficult to establish
  - Current standards require 3 repeatable tests

# Multiple breath washout testing in adults with pulmonary disease and healthy controls – can fewer measurements eventually be more?

Frederik Trinkmann  , Johannes Götzmann, Daniel Saur, Michele Schroeter, Katharina Roth, Ksenija Stach, Martin Borggreffe, Joachim Saur, Ibrahim Akin and Julia D. Michels

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- 153 patients – Conventional lung functions and MBW
- 3 measurements in 103 patients

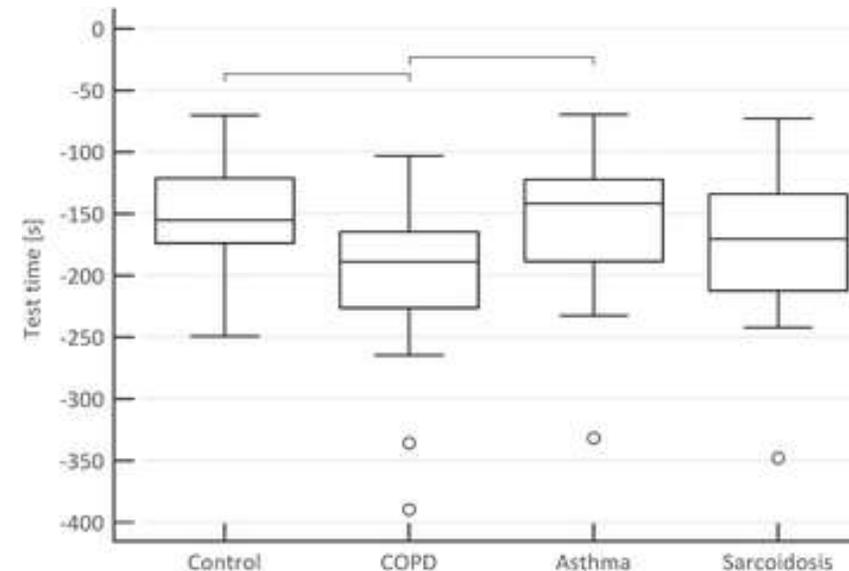
Subjects	LCI
Controls	7.4 ± 0.8
Sarcoidosis	8.1 ± 1.2
COPD	10.8 ± 2.2
Asthma	9.2 ± 1.9

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- Duplicate - LCI remained stable in all groups
- Mean absolute changes (modulus) -  $0.9 \pm 0.8\%$  in controls  $1.5 \pm 0.9\%$  in COPD,  $1.1 \pm 0.8\%$  in sarcoidosis and  $1.3 \pm 0.7\%$  in asthma, respectively
- Mean test time reduction differed significantly between groups reaching 200 s in COPD ( $p = 0.01$ )



# Normative LCI data

- The consistency of results with SF6 washout between centres and different equipment set-ups makes it a very attractive index for monitoring respiratory status
- N2 based normative data – from older studies and it is hypothesized new analysis may be more accurate

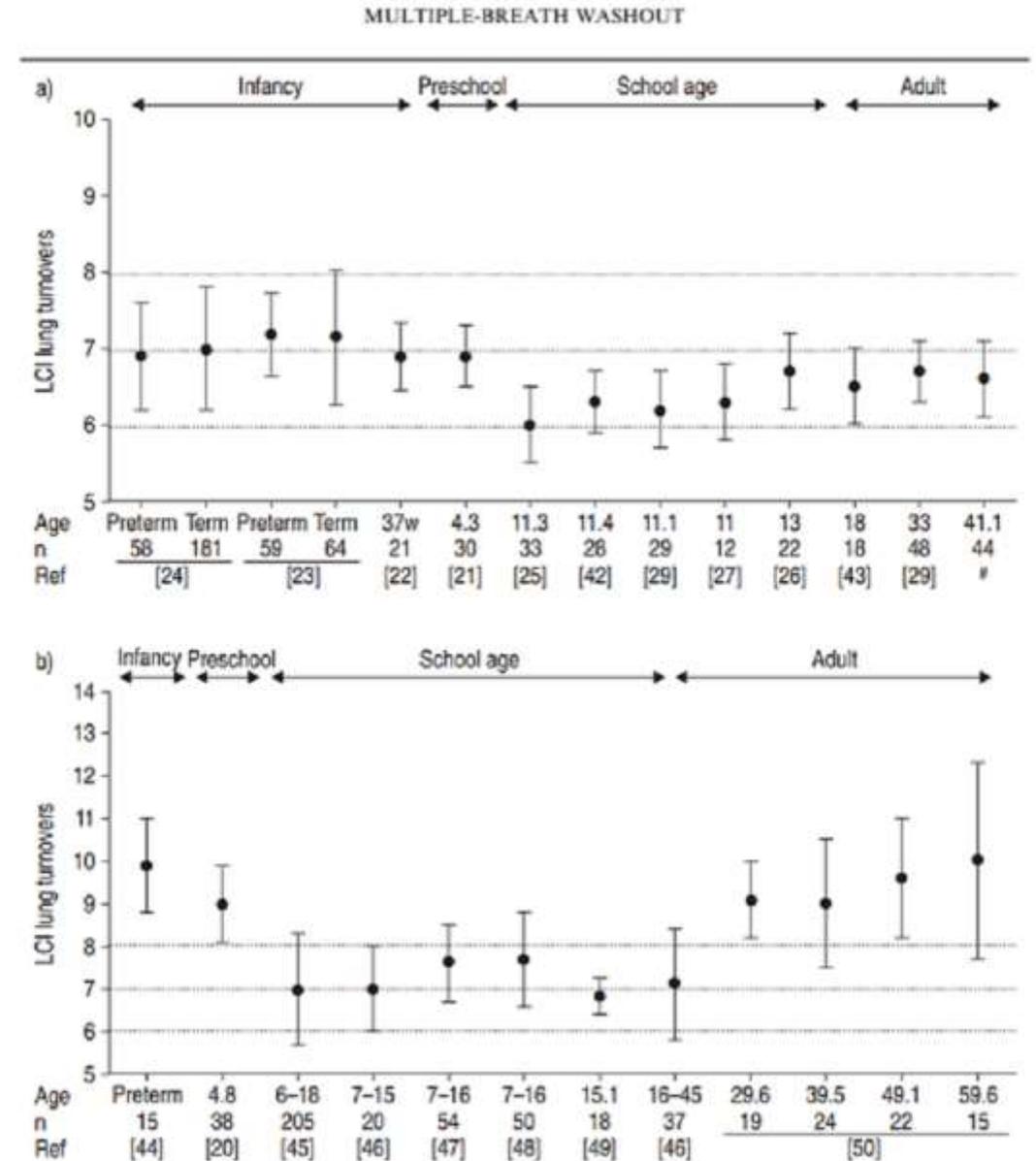


Fig. 2. – Normative values for lung clearance index (LCI) from multiple-breath washout using a) sulphur hexafluoride and b) nitrogen as the inert gas. Data are displayed as means with standard deviation bars. Data are arranged chronologically (mean age of cohort, in yrs unless otherwise stated). w: weeks. #; P.M. Gustafsson; unpublished data. -----; visual reference guides.

# Evaluation of ventilation maldistribution as an early indicator of lung disease in cystic fibrosis

- Spirometry findings (FEV1 and MEF25) v/s indices of ventilation inhomogeneity mixing ratio (MR) and LCI from MBW
- 43 CF patients v/s 28 healthy controls (3-18 years)
- 10/43 CF subjects (23%) reduced FEV1 and 14/34 (41%) low MEF25
- MR high in 31/43 (72%) and LCI in 27/43 (63%)
- MR was abnormal in 22/33 CF subjects with normal FEV1 versus 0/28 controls ( $p < 0.01$ )
- Abnormal MR was found in 10/20 CF subjects with normal MEF25 versus 0/22 controls

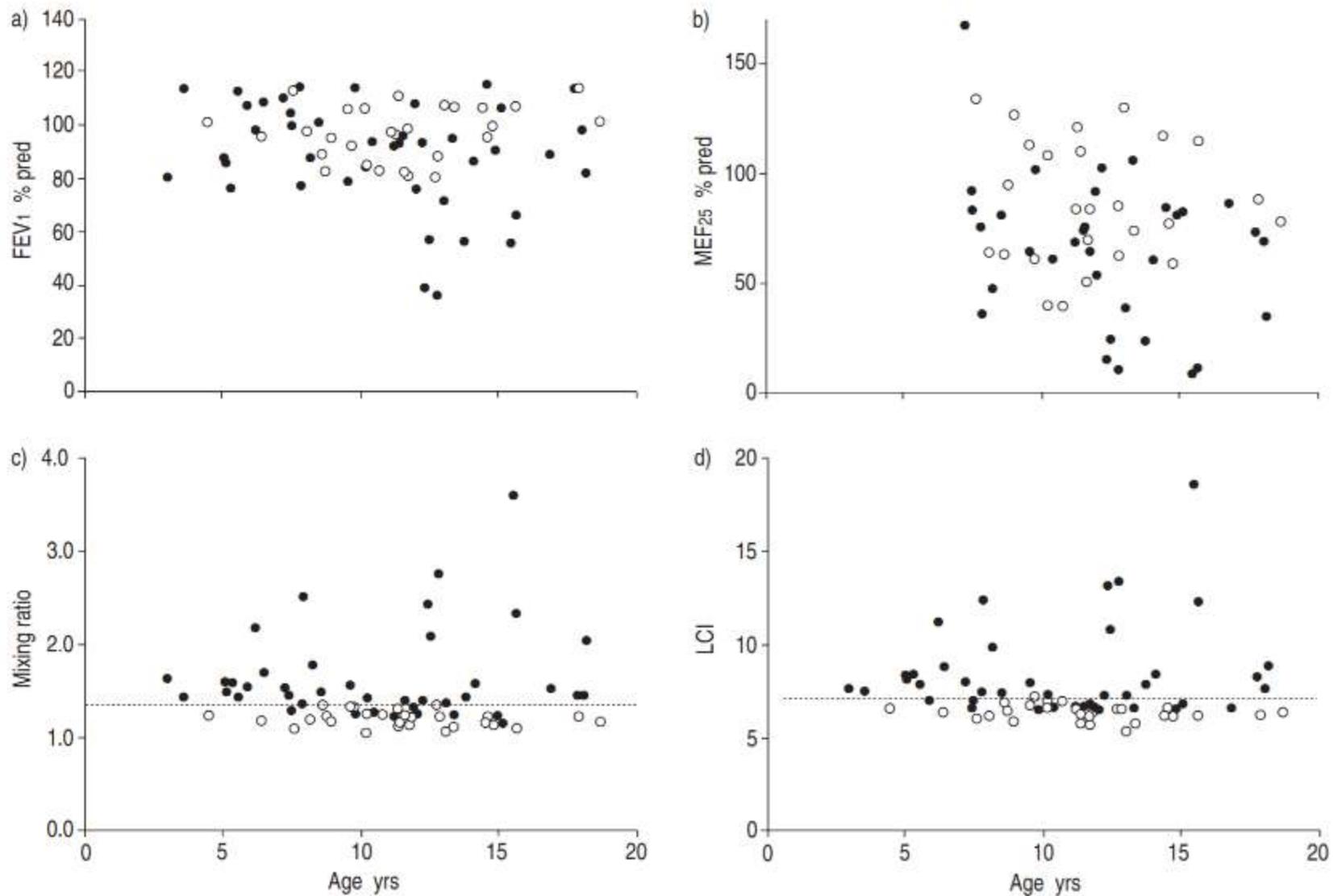


Fig. 1.—a) Forced expiratory volume in one second (FEV<sub>1</sub>) % predicted *versus* age in 43 patients with cystic fibrosis (CF) (●) and 28 healthy controls (○). b) Maximum expiratory flow at 25% of forced vital capacity (MEF<sub>25</sub>) % pred *versus* age in 34 patients with CF (●) and 26 healthy controls (○). c) Mixing ratio from multiple-breath washout (MBW) *versus* age in 43 patients with CF (●) and 28 healthy controls (○). d) Lung clearance index (LCI) from MBW *versus* age in 43 patients with CF (●) and 28 healthy controls (○). The dashed horizontal lines in figures c and d denote the upper limits of normality for mixing ratio (1.35) and LCI (7.17), respectively.

- Ventilation inhomogeneity detected in one-half to two-thirds of CF subjects with normal spirometry or RV/TLC results,
- Almost all CF children aged < 10 yrs who had normal FEV1 had abnormal LCI and MR
- Abnormal gas mixing found in virtually all CF patients with abnormal spirometry findings, abnormal RV/ TLC ratios, chronic bacterial airway colonisation, in two-thirds of those not colonized
- CF lung disease start early in childhood and long before it becomes evident with the methods currently used for monitoring of lung function
- MR and LCI are both sensitive and specific with respect to CF airway disease.

## 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

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**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.

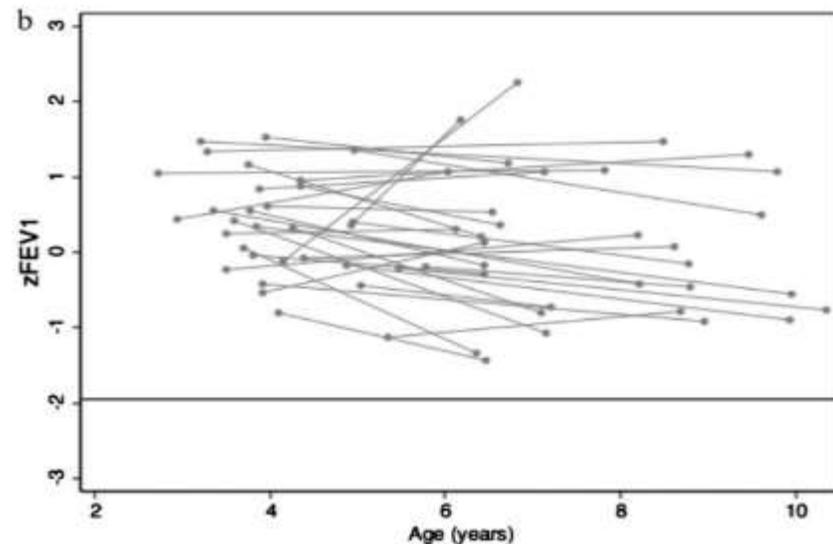
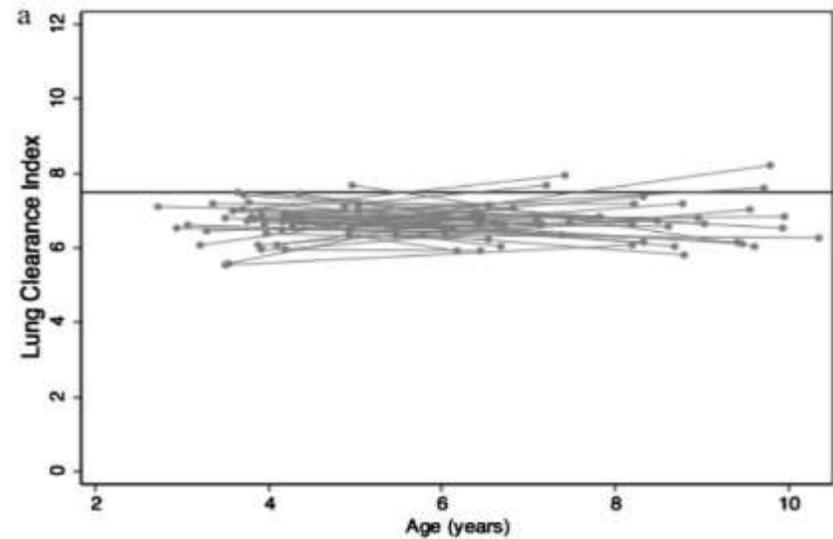
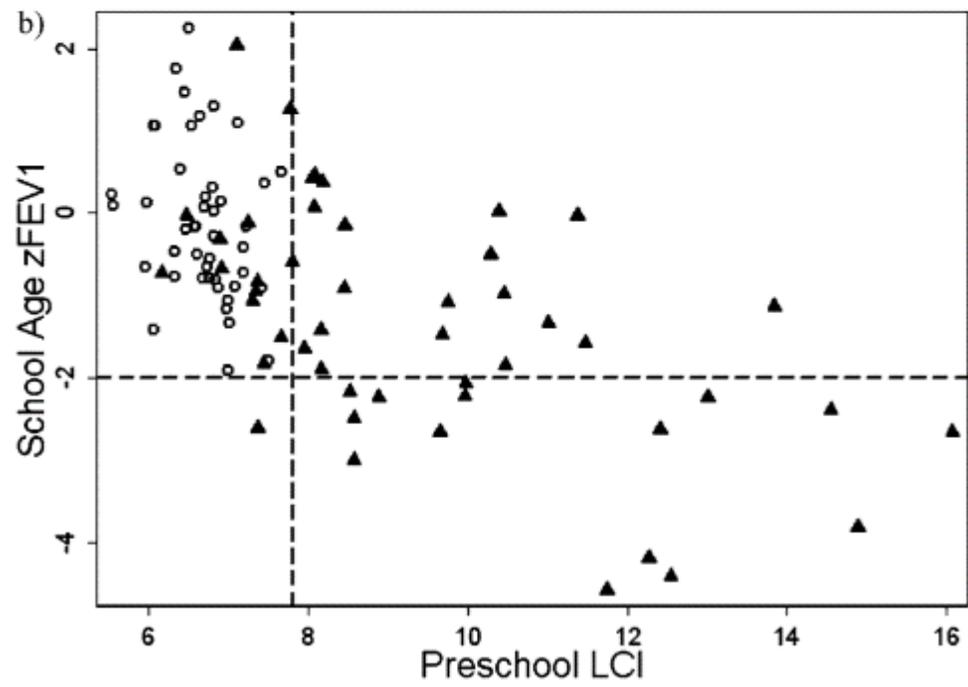
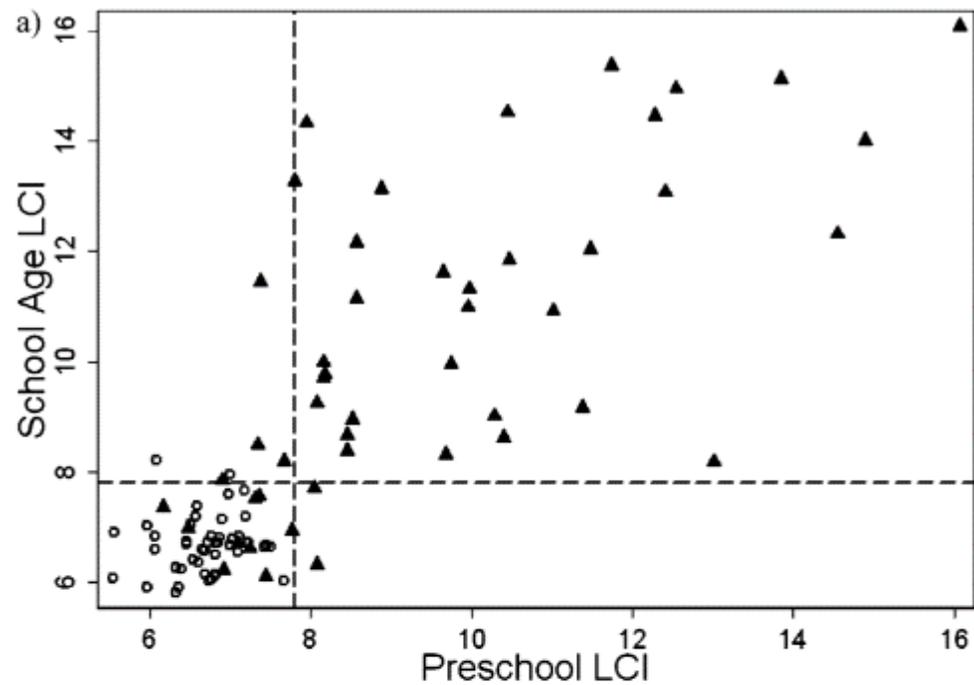
**Methods:** Forced expiratory volume in 1 second (FEV<sub>1</sub>) and maximal expiratory flow when 25% of forced vital capacity remains to be expired (MEF<sub>25</sub>) were compared with the lung clearance index (LCI) derived from sulphur hexafluoride MBW in 22 children with CF aged 6–16 years and 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<sub>1</sub> and MEF<sub>25</sub> 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<sub>1</sub> ( $r^2 = 0.62$ ) and MEF<sub>25</sub> ( $r^2 = 0.46$ ). However, while normal ( $\geq -1.96$  z-scores) FEV<sub>1</sub> and MEF<sub>25</sub> 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),  $p = 0.38$ ).

**Conclusions:** MBW is reproducible between laboratories, generates normal ranges which are constant over childhood, and is more frequently abnormal than spirometry in children with CF.

# Lung Clearance Index at 4 Years Predicts Subsequent Lung Function in Children with Cystic Fibrosis

- Prospective study
- 3–5 yr with CF and healthy control spirometry and MBW with testing repeated 6–10 yr.
- Primary outcomes FEV1 and LCI
- 73% children with CF had abnormal LCI at preschool age, whereas 5 had abnormal FEV1
- PPV of preschool LCI for predicting abnormal school-age result was 94%, NPV 62%.
- his suggests that abnormal
- LCI in young children with CF is a sensitive marker of early lung disease, rather than an epiphenomenon without clinical significance



**Figure 2.** Longitudinal changes in lung clearance index (LCI) and zFEV<sub>1</sub> for healthy children. (A) LCI remains stable in health with an upper limit of normal of 7.8. The median difference between tests was 0.0, with 95% of control subjects having an LCI at school age that was within  $\pm 1.3$  of the value recorded up to 7 years earlier during the preschool years. (B) The average change in zFEV<sub>1</sub> over time in healthy control subjects was  $-0.24$  (95% limits of agreement ranging from  $-1.8$  to  $1.3$ ).

<b>Author</b>	<b>Study type</b>	<b>n</b>	<b>Subjects</b>	<b>Findings</b>
<b>Hoo <i>et al</i></b>	Cross sectional	71	Infants	Higher LCI and FRC in infants with CF compared with 71 controls
<b>Aurora <i>et al</i></b>	Cross sectional	40	2.5-5 years	Higher LCI in patients with CF compared with 37 controls
<b>Aurora <i>et al</i></b>	Prospective	48	3-5 years and 6-10 years	Higher LCI in CF patients at preschool age compared with 45 controls. Preschool LCI predicted abnormal LCI in CF patients at school age
<b>Stanojevic <i>et al</i></b>	Prospective	78	2.5-6 years	LCI measurements in CF patients and 70 controls at 1, 3, 6 and 12 months detected lung function deterioration over time in CF patients
<b>Owens <i>et al</i></b>	Cross sectional	60	7 years	Higher LCI in CF compared to healthy controls
<b>Gustafsson <i>et al</i></b>	Cross sectional	43	3-18 years	Higher LCI and MR compared with 28 controls
<b>Poncin <i>et al</i></b>	Cross sectional	47	9-16 years	LCI higher in CF patients compared with 50 controls Poor agreement of LCI different setups

# LCI during infections and beyond

- 108 infants studied at diagnosis, 12 months 24 months
- BAL and SF6 (LCI/MR)
- Significant pulmonary infection ( $\geq 10^5$  cfu·mL<sup>-1</sup>) was associated with increased LCI
- Infants with a significant pulmonary infection at the time of MBW showed increases in lung clearance index (LCI) of 0.400 units (95% CI 0.150–0.648;  $p=0.002$ ). The impact was long lasting, with previous pulmonary infection leading to increased ventilation inhomogeneity over time compared to those who remained free of infection ( $p<0.001$ )
- symptoms, nor severe genotype were associated with increased LCI or moment ratios

# Effect of current pulmonary infections on LCI

	LCI	
	Difference	p-value
<b>Pulmonary infection</b>		
No infection	Reference	
Any infection excluding MOF	0.211 [0.031–0.391]	0.102
MOF only	0.125 [–0.052–0.302]	0.168
Significant infection excluding MOF $\geq 10^5$ cfu·mL <sup>-1</sup>	0.400 [0.150–0.648]	<b>0.002</b>
Any infection with a pro-inflammatory pathogen	0.270 [0.063–0.476]	<b>0.011</b>
<i>Aspergillus</i> spp. infection	0.738 [0.359–1.112]	<b>&lt;0.001</b>
<i>Haemophilus influenzae</i> infection	0.483 [0.154–0.811]	<b>0.004</b>
<i>Pseudomonas aeruginosa</i> infection	–0.059 [–0.479–0.361]	0.783
<i>Staphylococcus aureus</i> infection	0.054 [–0.253–0.360]	0.732
<b>Pulmonary inflammation</b>		
TCC $\times 10^3$ ·mL <sup>-1</sup> (for a doubling)	0.084 [–0.008–0.160]	<b>0.030</b>
Neutrophils $\times 10^3$ ·mL <sup>-1</sup> (for a doubling)	0.039 [–0.007–0.085]	0.095
NE level (for a doubling)	0.026 [–0.043–0.095]	0.464
Presence of NE	–0.017 [–0.271–0.237]	0.898
IL-8 level (for a doubling)	0.020 [–0.006–0.028]	0.228
Presence of IL-8	0.155 [–0.085–0.395]	0.206
Inflammatory response score	0.029 [–0.030–0.088]	0.343
Cumulative mean inflammatory response score	0.013 [–0.062–0.090]	0.729
<b>Clinical characteristics</b>		
Respiratory symptoms	0.025 [–0.190–0.240]	0.818
Severe genotype	0.097 [–0.183–0.377]	0.498

# Longitudinal effects of infection and inflammatory parameters on LCI

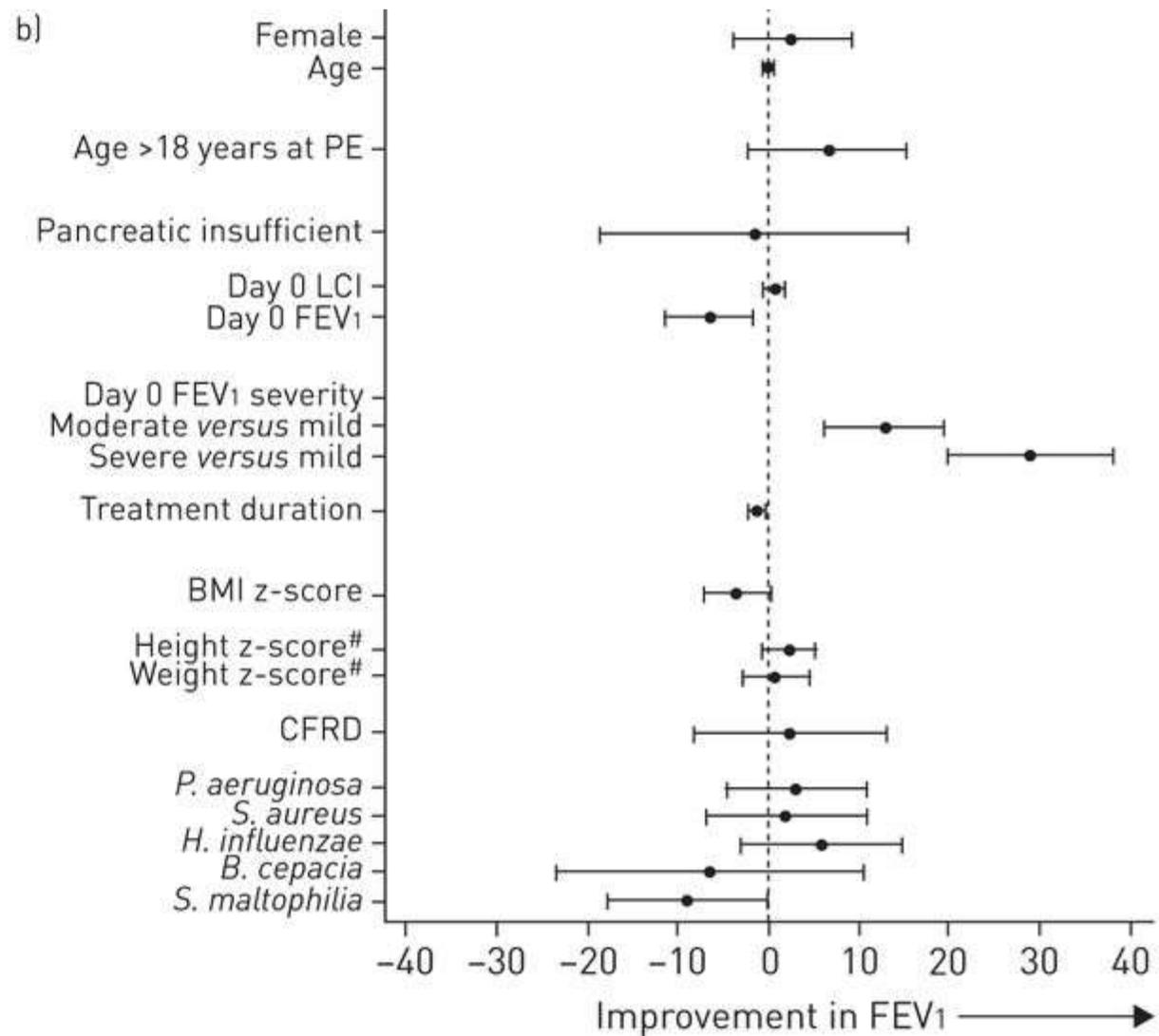
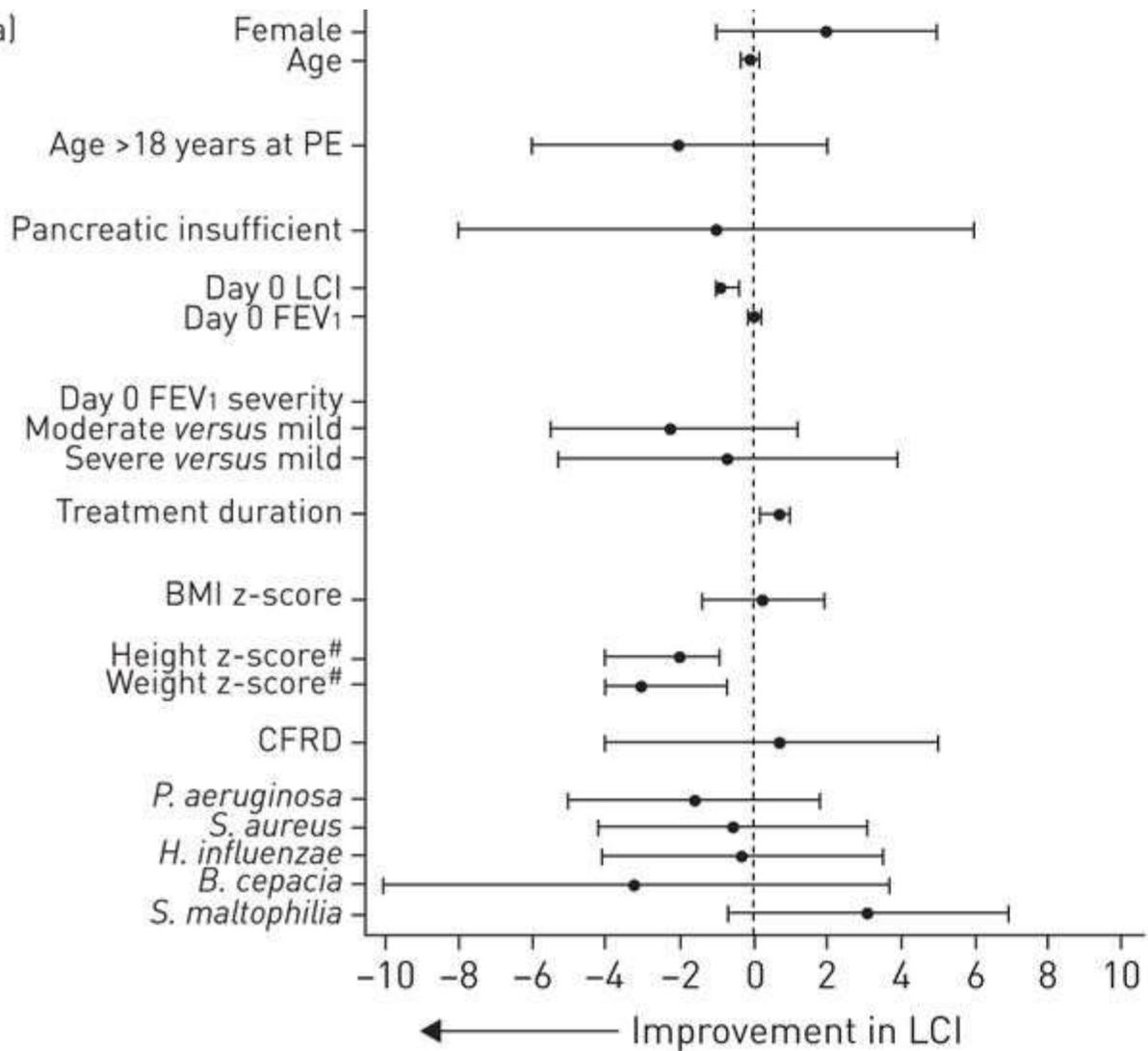
	LCI	
	Interaction between infection status and age (95% CI)	p-value <sup>#</sup>
Never infected	Reference	
Current infection and no past infection	0.361 [−0.06–0.768]	0.082
Current infection and past infection	0.656 [0.180–1.132]	<b>0.007</b>
No current infection and past infection	0.699 [0.061–1.337]	<b>0.032</b>
Infection with any pro-inflammatory pathogen	0.449 [0.160–0.738]	<b>0.002</b>
<i>Aspergillus</i> spp.	−0.044 [−0.619–0.531]	0.882
<i>Haemophilus influenzae</i>	1.069 [0.548–1.591]	<b>&lt;0.001</b>
<i>Pseudomonas aeruginosa</i>	0.087 [−0.561–0.736]	0.792
<i>Staphylococcus aureus</i>	0.343 [−0.016–0.702]	0.061
Absence of free NE	Reference	
Presence of free NE	0.204 [−0.125–0.533]	0.225
Absence of IL-8	Reference	
Presence of IL-8	0.066 [−0.432–0.564]	0.796
Non-severe genotype	Reference	
Severe genotype	0.374 [−0.073–0.821]	0.101

# Effect of infections on LCI in patients with Cystic Fibrosis

Author	Study type	n	Subjects	Findings
Belessis et al	Cross sectional	47	3months-3years	LCI of 25 healthy subjects was lower compared with CF patients without and with bacterial infection. In CF patients, inflammatory markers from BAL correlated with LCI
Singer et al	Prospective	78	4-16 years	LCI was higher in CF patients compared with 53 controls. LCI strongly correlated with Pseudomonas aeruginosa infection
O'Neill et al	Cross sectional	48	8 -67 years	LCI was higher in CF patients compared with 6 controls. A lower colony count of aerobic/anaerobic bacteria was associated with a higher LCI in CF patients

# LCI in cystic fibrosis subjects treated for pulmonary exacerbations

- Retrospective analysis - 176 pulmonary exacerbations in both paediatric and adult patients included
- Median LCI was 13.7
- treatment duration was 14 days (8–31 days)
- time between MBW measurements was 12 days (7–29 days)
- LCI decreased by 0.40 units (95% CI -0.60– -0.19,  $p=0.004$ ) or by 2.5% following treatment with antibiotics FEV1 increased by 14% (95% CI 10–17%) overall





# Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial

*Jane Davies, Helen Sheridan, Nicholas Bell, Steve Cunningham, Stephanie D Davis, J Stuart Elborn, Carlos E Milla, Timothy D Starner, Daniel J Weiner, Po-Shun Lee, Felix Ratjen*

- CF patients G551D mutation
- FEV1 > 90% predicted
- > 6years
- LCI > 7.4
- Ivacaftor v/s placebo
- Primary outcome was change in LCI
- Secondary – FEV1%pred, Sweat Chloride conc and CF Q



# Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-CFTR mutation and preserved spirometry: a randomised controlled trial

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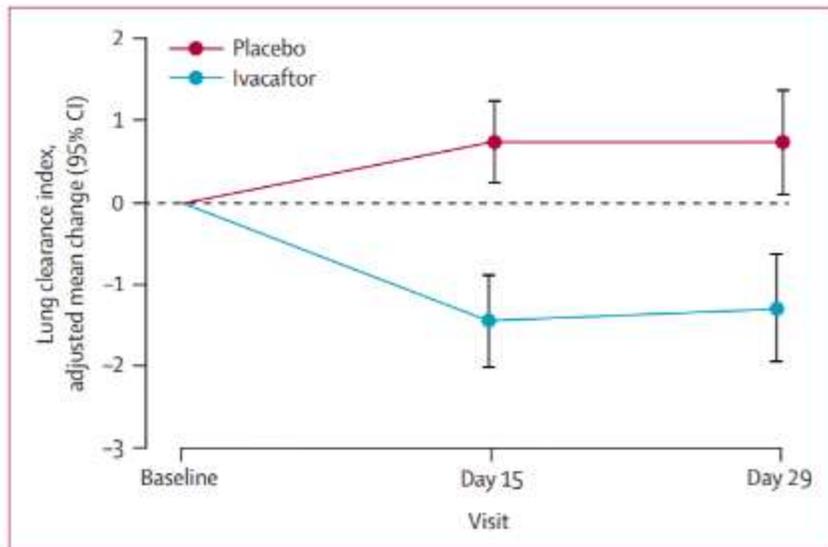


Figure 2: Mean change from baseline in lung clearance index

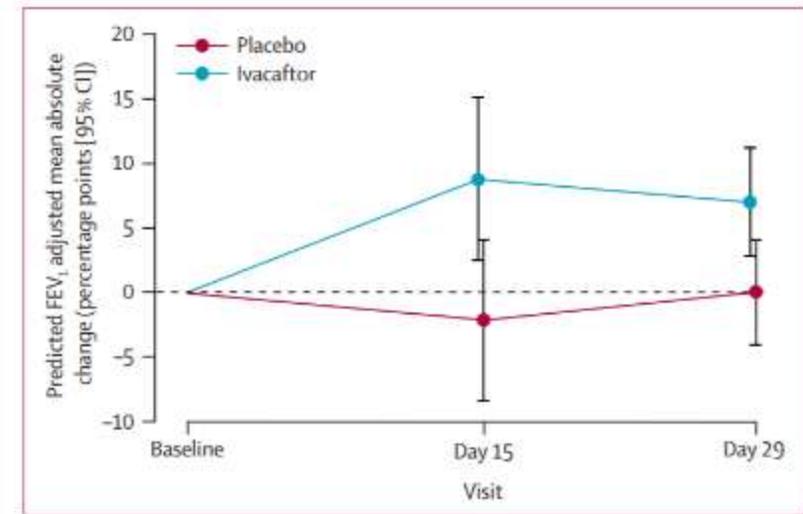


Figure 3: Mean change from baseline in percent predicted FEV<sub>1</sub>. FEV<sub>1</sub>=forced expiratory volume in 1 s.

The mean reduction in LCI - greater with ivacaftor treatment than with placebo at all study assessments (difference between groups in the average of mean changes from baseline at days 15 and 29 was  $-2.16$  [95% CI  $-2.88$  to  $-1.44$ ]  $p < 0.001$ )

Mean reduction in %predFEV<sub>1</sub> was significantly greater with ivacaftor treatment (difference in the average of mean changes at day 15 and day 29 was  $8.67$  percentage points [95% CI  $2.36$ – $14.97$ ];  $p = 0.0103$ )

# Assessment of treatment benefit using LCI

<b>Author</b>	<b>Study type</b>	<b>n</b>	<b>Subjects</b>	<b>Findings</b>
<b>Subbarao <i>et al</i></b>	Observational	25	1-5 years	Treatment with hypertonic saline BD improved LCI
<b>Amin <i>et al</i></b>	Observational	19	>10years	Improvement in LCI
<b>Amin <i>et al</i></b>	Clinical trial	17		Inhaled pulmozyme improvement in LCI
<b>Milia <i>et al</i></b>	Clinical trial	58	6-11 years	Improvement in LCI, sweat chloride and nutritional status

# Summary

- MBW abnormalities – marker of early lung involvement in CF
- Can differentiate patient with CF from healthy controls even in presence of normal spirometry
- Can predict progression of lung disease in CF
- May be an important modality assessing treatment outcomes to therapy and effect of infective exacerbations

# MBW in Bronchial asthma

- Significant ventilation inhomogeneity expected as a result of inflammation and remodelling
- Spirometry insensitive in the assessment of peripheral airways, unless severe obstruction present
- LCI can help assessing small airway involvement
- LCI in asthmatic subjects slightly elevated compared with healthy controls, but often within the normal range hence not a diagnostic modality
- Heterogeneity may predict airway hyperresponsiveness

# Ventilation heterogeneity is a major determinant of airway hyperresponsiveness in asthma, independent of airway inflammation

- 40 patients
- Airway inflammation by exhaled nitric oxide
- Ventilation heterogeneity by multiple breath nitrogen washout
- Airway hyperresponsiveness by methacholine challenge were expressed as DRR
- Those with suboptimal control (18) were treated and tests were repeated

# Ventilation heterogeneity is a major determinant of airway hyperresponsiveness in asthma, independent of airway inflammation

- Significant correlation between DRR and ventilation heterogeneity in conductive airways
- Between DRR and airway inflammation (FeNO)
- Negative correlation with %predFEV1 and FEV1/FVC ratio
- Post treatment also significant correlation between DRR and conductive airway inhomogeneity as measured with MBW

# Ventilation heterogeneity is a major determinant of airway hyperresponsiveness in asthma, independent of airway inflammation

**Table 2** Pearson correlation coefficients (r) of baseline variables with airway hyperresponsiveness (dose response ratio, DRR) for the asthmatic group as a whole and for the treatment subgroup before and after treatment

	Baseline asthma group (n=40)		Baseline treatment subgroup (n=18)		Post-treatment treatment subgroup (n=18)	
	r	p Value	r	p Value	r	p Value
Airway inflammation (FE <sub>NO</sub> )	0.62	<0.001	0.51	0.03	0.61	0.008
Ventilation heterogeneity (S <sub>cond</sub> )	0.63	<0.001	0.64	0.004	0.82	<0.001
Ventilation heterogeneity (S <sub>acin</sub> )	0.07	0.67	0.04	0.86	-0.02	0.93
Ventilation heterogeneity (LCI)	0.38	0.02	0.31	0.21	0.47	0.05
FEV <sub>1</sub> % predicted	-0.44	0.005	-0.40	0.10	-0.37	0.13
FEV <sub>1</sub> /FVC ratio	-0.47	0.002	-0.34	0.17	-0.21	0.41

FEV<sub>1</sub>, forced expiratory volume in 1 s; FE<sub>NO</sub>, fraction of nitric oxide in exhaled breath; FVC, forced vital capacity; LCI, lung clearance index; S<sub>cond</sub>, ventilation heterogeneity in conducting airways; S<sub>acin</sub>, ventilation heterogeneity in acinar lung zone

# Ventilation heterogeneity is a major determinant of airway hyperresponsiveness in asthma, independent of airway inflammation

- $S_{\text{cond}} = 0.037/l$  good combination of sensitivity and specificity (71.9% and 90.0%, respectively) for detecting the presence of AHR
- First study to demonstrate ventilation heterogeneity in the conducting airways is a significant predictor of AHR in subjects with asthma, independent of airway inflammation as measured by exhaled nitric oxide, both before and after ICS treatment
- Ventilation heterogeneity is an important contributor to AHR in asthma. The index  $S_{\text{cond}}$  derived from the MBW is a measure of conducting airway function that is likely to be useful in the clinical management of asthma and for the assessment of new treatment strategies and drugs in this disease

# MBW predicts peripheral airway dysfunction in asthma

- A cohort of 196 adults (median (range) age 44 (18–61) years, 109 females, 54 ex-smokers, six current smokers) with physician-diagnosed asthma .
- Subjects – clinical interviews, questionnaires, skin prick tests (SPT) and blood eosinophil counts. Lung function was assessed by spirometry, impulse oscillometry (IOS) and nitrogen multiple breath washout (N<sub>2</sub> MBW)
- Peripheral airway dysfunction was detected in 31% by FOT to 47% (Scnd x VT) of subjects. Risk factors for peripheral airway dysfunction were identified.
- Among subjects with low FEV1 and either positive smoking history and/or blood eosinophilia (>4.0%), 63% had abnormality across all peripheral airway outcomes

# Clinical significance of small airway obstruction markers in patients with asthma

- Seventy-four adults with asthma and 18 healthy control subjects underwent FOT, multiple breath inert gas washout (MBW), body plethysmography, single-breath determination of carbon monoxide uptake and spirometry
- small airway obstruction markers Sacin , resistance at 5 Hz minus resistance at 20 Hz (R5-R20) and reactance area (AX) were not independently associated with asthma severity, control, quality of life or exacerbations
- markers of total (R5) and mean airway resistance of large and small airways (R20) significantly higher in the severe asthma group vs mild-moderate group (0.47 vs. 0.37,  $P < 0.05$  for R5; 0.39 vs. 0.31,  $P < 0.01$  for R20)

# Ventilation heterogeneity predicts asthma control in adults following inhaled corticosteroid dose titration

- Adult asthmatic patients had the ACQ scores and lung function measured at baseline and after 8 weeks
- PFT – Spirometry, MBW
- The dose of ICS was doubled if the ACQ score was greater than or equal to 1.5 (uptitration) and quartered if the ACQ score was less than 1.5
- relationships between baseline physiological parameters and the change in the symptom-only 5-item ACQ (deltaACQ-5) were examined

# Ventilation heterogeneity predicts asthma control in adults following inhaled corticosteroid dose titration

- Ventilation heterogeneity in convection-dependent airways ( $r = -0.64$ ;  $P = .002$ ) correlated with deltaACQ-5
- Heterogeneity in convection-dependent airways was independent predictor ( $r^2 = 0.34$ ;  $P = 0.007$ )
- ICS dose down titration ( $n = 41$ ) worsened ACQ-5 scores (0.46 to 0.80;  $P < .001$ ), with 29% of the patients having a deltaACQ-5 of greater than 0.5. Only baseline ventilation heterogeneity in diffusion-dependent airways correlated with deltaACQ-5 ( $r = 0.40$ ;  $P = .009$ )
- Increased ventilation inhomogeneity at baseline is associated with improvement following inhaled corticosteroid dose up titration

# MBW – Asthma

- Presence of small (peripheral airway involvement)
- Determinant of airway hyper responsiveness
- Predictor of response to steroid
- May not correlate with severity

# COPD

- Characterised by a variable combination of airway and parenchymal abnormalities
- hallmark is irreversible airflow obstruction resulting from the narrowing of small conducting airways or loss of lung elastic recoil or both
- MBW measurements have the potential to diagnose subclinical disease at an earlier stage

# Feasibility and challenges of using multiple breath washout in COPD

- 54 COPD patients – MBW Spirometry Body plethysmography
- Mean age 66 Smoking – 42 pack years 31% frequent exacerbators
- 4 patients were unable to perform MBW
- Repeatability: Triplicate testing – CV repeatability on same day 4.1 (2.2-7) for LCI
- No significant difference in LCI repeated in triplicate after 13-16 days

# Feasibility and challenges of using multiple breath washout in COPD

- Comparison of LCI with other lung physiology assessments –
  - $LCI_{N_2}$  was raised in all patients with COPD
  - Inverse correlation with FEV<sub>1</sub>
  - $LCI_{N_2}$  also increased significantly with greater GOLD stage GOLD 1-10.2 GOLD 2-11.9 GOLD 3-14.19
  - FRC values MBW vs plethysmography – Higher  $FRC_{N_2}$
  - Mean difference between  $FRC_{N_2}$  and  $FRC_{pleth}$  was 14.8% predicted
- LCI offers substantial promise as a measurement in COPD
- LCI measure of early airways disease in those with well-preserved FEV<sub>1</sub>

# Peripheral airway dysfunction and relationship with symptoms in smokers with preserved spirometry

- 80 current / ex smokers of >5 pack-years and no history of past/present cardiac and respiratory diseases were recruited from the community
- Normal spirometry
- Symptoms – chronic bronchitis, wheeze, dyspnea
- spirometry, body plethysmography, DLCO, FOT and MBNW

# Peripheral airway dysfunction and relationship with symptoms in smokers with preserved spirometry

- Results – 18 ex smokers, 62 current smokers
- Normal lung volumes and DLCO
- 39% Chronic bronchitis
- 49% wheeze 38% Dyspnea
- Subjects chronic bronchitis higher Scond (Z-score 0.54 (−0.22–2.58) vs 0.24 (−0.54–1.16); P = 0.043)
- Dyspnea had a borderline lower postbronchodilator FEV1 % predicted (99.1 (11.1) vs 104.3 (11.6); P = 0.06)
- Wheeze had higher R5 and lower FEV1% predicted
- No differences smoking history, age, gas trapping between those who reported symptoms versus asymptomatic

**Table 3** Cross tabulations of the number of subjects with abnormalities in ventilation heterogeneity and respiratory impedance

	Abnormal R5/X5		Total
	Yes	No	
Abnormal Sacin/Scond			
Yes	21	19	40
No	20	20	40
Total	41	39	80

R5, respiratory resistance at 5 Hz; X5, reactance at 5 Hz.

# Peripheral airway dysfunction and relationship with symptoms in smokers with preserved spirometry

- Respiratory symptoms and peripheral airway dysfunction are common in smokers with normal spirometry
- Symptoms of chronic bronchitis related to conductive airway abnormalities, while wheeze was related to spirometry and IOS
- Clinical significance remains to be determined

# The Association of Lung Clearance Index with COPD and FEV1 Reduction in 'Men Born in 1914'

- Population based study - LCI predicts pulmonary obstruction and incidence of chronic obstructive pulmonary disease (COPD) events over a long-term follow-up
- Multiple breath nitrogen washout and spirometry were performed in 674 men from the cohort "Men born in 1914" at age 55 years
- classified into quartiles of LCI and according to LCI above and below ULN
- Incidence of COPD events (COPD hospitalisations or COPD-related deaths) were monitored over the remaining life span of the men, by linkage with national hospital registers
- development of pulmonary obstruction studied in men who were re-examined with spirometry at 68 years

# The Association of Lung Clearance Index with COPD and FEV1 Reduction in 'Men Born in 1914'

- Median LCI was 8.0 for the total sample (8.2 for smokers and 7.6 for nonsmokers). The proportion of current and ever smokers increased as LCI increased. Mean FEV1 was lowest in quartiles with higher LCI
- All-cause mortality rates were significantly higher in men with poor LCI
- A total of 85 men had COPD diagnosed during the follow-up period of 1969–2013
- The adjusted HR was 2.24 (CI:1.3–3.9), comparing LCI>ULN with normal LCI
- The adjusted HR for COPD per 1 SD increase in LCI was 1.62 (CI:1.29–2.03)
- The relationship between LCI and incidence of COPD became slightly stronger after adjustment for smoking status, diabetes, BMI, height, and physical activity Q1 vs Q4 3.6

# The Association of Lung Clearance Index with COPD and FEV1 Reduction in 'Men Born in 1914'

**Table 2.** Incidence rates and hazard ratios of COPD by quartiles of LCI and LCI > ULN.

	Q1 (reference) 4.4–6.9	Q2 7.0–7.9	Q3 8.0–8.9	Q4 9.0–12.6	<i>p</i> , trend	Normal LCI (n = 589)	LCI > ULN (n = 85)
All-cause mortality, n (/1000 person years)	161 (40)	171 (42)	171 (44)	168 (49)		586 (43)	85 (54)
All-cause mortality adjusted (95% CI) <sup>a</sup>	1.00	1.04 (0.83–1.3)	1.08 (0.87–1.35)	1.52 (1.2–1.9)	<0.001	1.00	1.78 (1.41–2.24)
COPD events, n (/1000 person years)	12 (3.1)	16 (4.0)	22 (5.9)	35 (10.9)	—	69 (5.2)	16 (10.6)
COPD events, unadjusted (95% CI)	1.00	1.30 (0.61–2.74)	1.97 (0.97–3.98)	3.99 (2.06–7.71)	<0.001	1.00	2.37 (1.36–4.10)
COPD events, adjusted (95% CI) <sup>a</sup>	1.00	1.21 (0.56–2.59)	1.73 (0.85–3.52)	3.40 (1.74–6.67)	<0.001	1.00	2.24 (1.29–3.92)
COPD events, adjusted (95% CI) <sup>a,b</sup>	1.00	1.18 (0.55–2.53)	1.63 (0.80–3.32)	2.34 (1.17–4.69)	0.006	1.00	1.85 (1.05–3.27 <sup>a,c</sup> )

SD, standard deviation.

<sup>a</sup> Adjusted for smoking status (three groups: never, ex and current smokers), diabetes, BMI, height, and physical activity (three groups: high, moderate and low physical activity).

<sup>b</sup> Additionally adjusted for FEV<sup>1</sup> or

# The Association of Lung Clearance Index with COPD and FEV1 Reduction in 'Men Born in 1914'

**Table 3.** Hazard ratios of COPD by categories of FEV<sub>1</sub><sup>%pred</sup> and lung clearance index.

	Normal FEV <sub>1</sub> Normal LCI (Reference)	Normal FEV <sub>1</sub> LCI > ULN	FEV <sub>1</sub> < LLN Normal LCI	FEV <sub>1</sub> < LLN, LCI > ULN (Highest risk Category)	p value (3 df)
N (= 674)	535	60	54	25	
COPD events, unadjusted (95% CI)	1.00	1.48 (0.67–3.26)	3.05 (1.59–5.83)	7.36 (3.61–15.0)	<0.001
COPD events, adjusted (95% CI) <sup>a</sup>	1.00	1.36 (0.61–3.00)	*2.63 (1.35–5.12)	*7.81 (3.78–16.1)	<0.001

<sup>a</sup> Adjusted for smoking status (three groups: never, ex and current smokers), diabetes, BMI, height, and physical activity (three groups: high, moderate and low physical activity).

\*Difference between FEV<sub>1</sub> < LLN/Normal LCI and FEV<sub>1</sub> < LLN/LCI > ULN: p-value 0.019.

**Table 4.** Hazard ratios of COPD by categories of FEV<sub>1</sub>/VC and lung clearance index.

	Normal FEV <sub>1</sub> /VC Normal LCI (Reference)	Normal FEV <sub>1</sub> /VC LCI > ULN	FEV <sub>1</sub> /VC < LLN Normal LCI	FEV <sub>1</sub> /VC < LLN LCI > ULN (Highest risk Category)	p value (3 df)
N (= 674)	530	63	59	22	
COPD events, unadjusted (95% CI)	1.00	1.45 (0.62–3.38)	5.38 (3.16–9.15)	10.32 (5.16–20.6)	<0.001
COPD events, adjusted (95% CI) <sup>a</sup>	1.00	1.34 (0.58–3.19)	*5.15 (2.95–9.01)	*11.75 (5.79–23.8)	<0.001

<sup>a</sup> Adjusted for smoking status (three groups: never, ex and current smokers), diabetes, BMI, height and physical activity (three groups: high, moderate and low physical activity).

The categories are divided by FEV<sub>1</sub>/VC (normal vs < LLN) and LCI (normal vs > ULN).

\*Difference between FEV<sub>1</sub>/VC < LLN/normal LCI and FEV<sub>1</sub>/VC < LLN/LCI > ULN: p-value 0.041.

## [The application of multiple breath nitrogen washout in chronic obstructive pulmonary disease].

[Article in Chinese]

Liu B<sup>1</sup>, Zhou Q<sup>1</sup>, He B<sup>2</sup>.

### ⊕ Author information

#### Abstract

**OBJECTIVE:** We investigated ventilation inhomogeneity indices (Sacin, Scond) in patients with chronic obstructive pulmonary disease (COPD) using the multiple breath nitrogen washout test (MBNW) and determined the correlation between the 2 indices ( Scond and Sacin, as a measure of ventilation inhomogeneity in conductive and acinar zones of the lungs, respectively) and lung function to investigate the significance of assessing the COPD severity with ventilation inhomogeneity indices.

**METHODS:** Forty-three stable COPD patients and 56 non-smoking healthy subjects were recruited from November 2014 to February 2015. The differences of ventilation inhomogeneity indices (Sacin, Scond) between the 2 groups were compared, and the correlation between ventilation inhomogeneity indices and traditional parameters of lung function were determined using Pearson linear correlation. According to the FEV1%pred=50%, COPD patients were divided into 2 groups and ventilation inhomogeneity indices (Sacin, Scond) were compared between groups.

**RESULTS:** Compared with the healthy control group, Sacin [0.320 (0.238, 0.432) vs 0.097 (0.073, 0.144),  $u=144.5$ ,  $P<0.001$ ], and Scond [0.082 (0.043, 0.103) vs 0.018 (0.007, 0.028),  $u=103.5$ ,  $P<0.001$ ] in COPD patients were significantly increased, and the difference was statistically significant. Sacin and Scond were negatively correlated with FVC%pred ( $r=-0.686$ ,  $-0.551$ , both  $P<0.001$ ), FEV1%pred ( $r=-0.681$ ,  $-0.475$ , both  $P<0.01$ ), FEV1/FVC ( $r=-0.458$ ,  $-0.210$ , both  $P<0.01$ ). Sacin was negatively correlated with DLCO ( $r=0.413$ ,  $P<0.01$ ). With the increase in the severity of the disease, Sacin and Scond increased gradually.

**CONCLUSION:** Sacin and Scond in COPD patients increased significantly, which was significantly correlated with lung function. COPD has ventilation inhomogeneity in conductive and acinar zones and ventilation inhomogeneity indices can be used to evaluate the severity of COPD.

# MBW - COPD

- Raised LCI may predict small airway disease in symptomatic smokers with normal spirometry
- LCI and acinar and conductive airway heterogeneities are seen in COPD
- Increasing LCI in COPD may predict hospitalisations, exacerbation and mortality

**Abstract Group:** 8.2. Transplantation

**Keyword 1:** Monitoring **Keyword 2:** Lung function testing **Keyword 3:** Children

**Title:** Multiple breath washout in bronchiolitis obliterans syndrome following paediatric lung transplantation

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**Body:** Aim: Bronchiolitis obliterans syndrome (BOS) is a significant cause of morbidity and mortality following lung transplantation. Lung Clearance Index (LCI) measured by multiple breath washout (MBW) detects early structural lung damage in other paediatric obstructive lung disease. The aim was to determine the pattern of LCI values in children with BOS. Methods: Retrospective analysis of MBW and spirometry data from subjects transplanted between 2002-2010 (date of annual MBW testing introduction). BOS staging was defined using published "all age" reference equations. LCI in BOS 0, 0p and 1 were compared. Results: 50/56 (89%) subjects had MBW performed (n=162): mean (SD:range) 3.1 (1.85:1-9) times over a mean (SD: range) follow up 1069 (613: 196-2613) days. Abnormal LCI values (>7.5) were common post transplant (63/114 tests, 55%). LCI was increased in subjects with BOS. All those with persistent LCI>10 (n=8) died from severe BOS. Two distinct BOS patterns were seen: gradual vs. very rapid FEV1 decline. Despite infrequent testing, earlier LCI signal was seen in some (3/8) but not all 8 subjects (e.g. not those with rapid FEV1 decline).

	BOS stage post transplant			
	No BOS	Any BOS	BOS 0p	BOS ≥1
Number of MBW tests	70	46	38	8
LCI	7.34 (5.83-11.13)	7.90 (6.32-14.70)*	7.73 (6.32-13.14)*	12.3 (6.51-14.70)*Φ
LCI > 7.5	33/70 (47.1%)	32/46 (69.5%)	25/38 (65.8%)	7/8 (87.5%)

Data displayed as median (range). p<0.05 vs. \*No BOS or ΦBOS 0p

**Conclusion:** LCI is frequently abnormal post lung transplantation. LCI is significantly elevated in BOS, and appears to increase with BOS severity. An early signal of subsequent outcome may exist but optimal frequency of testing is yet to be determined.

LCI and MBW in BOS

# Multiple breath washout: A new and promising lung function test for patients with idiopathic pulmonary fibrosis.

- 5 IPF patients and 25 healthy controls were assessed at baseline and 10 patients at median 6.2 months later
- Outcomes LCI N<sub>2</sub> -MBW, forced vital capacity (FVC) DL<sub>CO</sub> , bronchiectasis score, the GAP stage and death or lung transplantation
- feasibility, repeatability, discriminative capacity and correlation with disease severity and structural lung damage – end points
- LCI was repeatable and reproducible. Median LCI in IPF 11.6 (10.1-13.8) in IPF versus 7.3 (6.9-8.4) in controls (P < 0.0001)
- LCI correlated with DLCO, GAP stage, Bronchiectasis score but not FVC
- 6 died LCI correlated with outcome with HR 2.43

# Limitations of MBW testing, knowledge gaps

- Time consuming 15-20 mins per patient (triplicate testing)
- LCI values from one platform may not be comparable with the other platform
- The impact of repeat LCI measurements on respiratory disease outcomes is largely unknown.
- It remains unclear what change in LCI should prompt clinicians to intervene

# Conclusion

- MBW sensitive for the early detection of lung function impairment often arising in small peripheral airways
- MBW is attractive lung function test young patients, as measurements require minimal cooperation
- mounting evidence that the LCI and heterogeneity indices are useful for assessing the extent and progression of lung disease, as well as treatment response, in patients with CF
- Application in other chronic lung diseases may be attractive for research
- The impact on clinical management and respiratory disease outcomes require further studies

# Forced oscillation techniques (FOT)

# Introduction

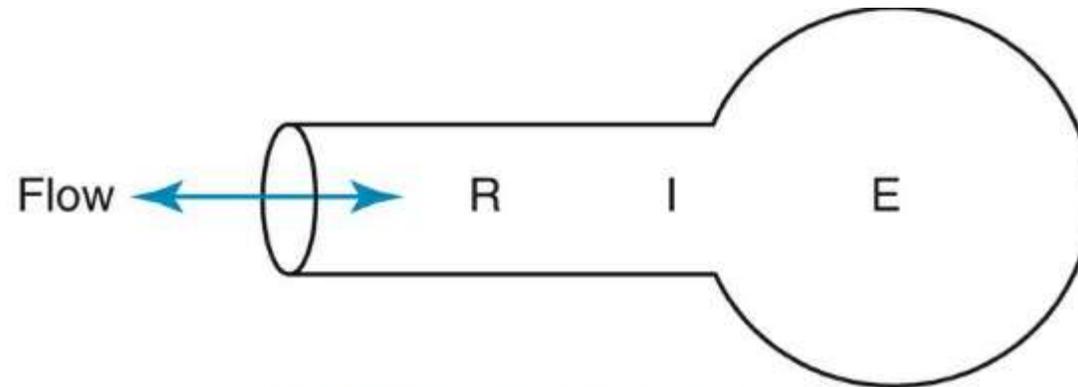
- FOT is particularly useful for measuring changes in the airways of patients who may be unable to perform spirometry or body plethysmography
- young children or those with physical limitations that prevent them from performing tests that require effort and coordination

# Principle

- Mechanical properties of the respiratory system are measured
- Apply an oscillating flow of gas to the system and measuring the resulting pressure response
- Oscillations – mouth or around the body in a closed body plethysmograph and resulting pressures are measured at the mouth
- Mechanical properties are measured – Impedance ( $Z_{rs}$ )
- Represents the net force that must be overcome to move gas in and out of the respiratory system (upper airway, lungs, and chest wall)

# Principle

- Pressure required to push gas down the pipe and into the balloon
- Pressure must overcome three basic forces: the resistance (R) of the pipe; the elastance (E), or stiffness, of the balloon; and the inertia (I) of the gas itself



**FIG. 10.7** Equation of motion.

Measuring the pressure, flow, and volume generated at the mouth during breathing, one can solve for the parameters resistance (R), elastance (E), and inertia (I) that define the mechanical characteristics of the model.

# Principle

$$\text{Pressure} = R (V^Y) + E (V) + I (V^{YY})$$

where:

$V$  = volume

$V^Y$  = flow

$V^{YY}$  = acceleration

- Impedance depends not only on these three variables, R, E, and I, but also on the frequency of the oscillation
- At low frequencies, I is negligible, R is less important, and E is dominant
- At higher frequencies, R and I become more important

# Principle

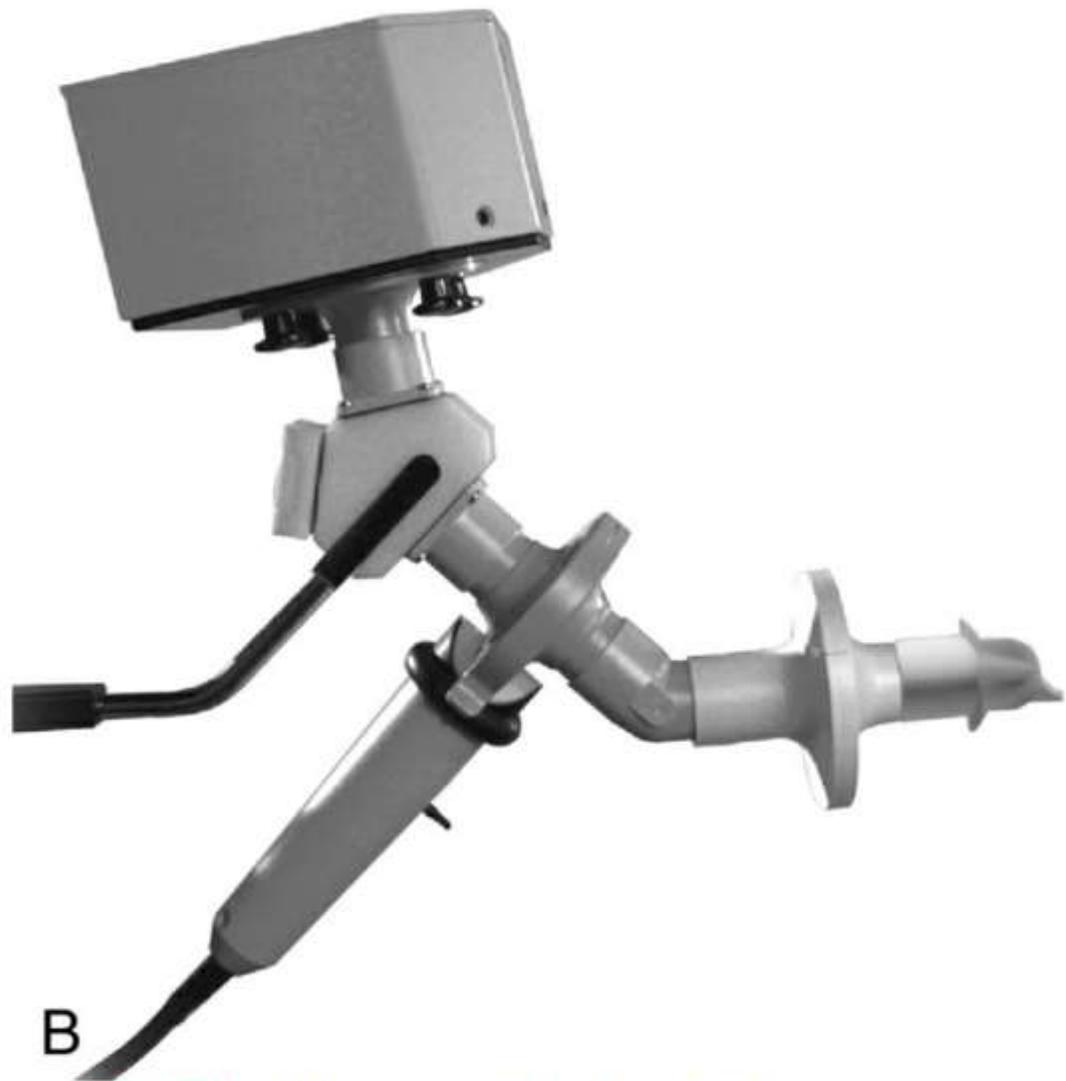
- To measure  $Z$ , apply flow at various single frequencies and measure the resulting pressures generated at each frequency
- Or apply a flow signal consisting of many different frequencies at once and then use complex mathematical functions to break down the output into unique sine waves, each of its own frequency
- Loudspeakers pulsating at different predetermined frequencies to generate the broadband flow signals
- Flow signals are applied on quiet tidal breathing

# Principle

- The output is recorded in two parts:
  - The part of  $Z$  that is in phase with the flow signal, which represents the real part of the  $Z$  and is caused by flow-resistive properties of the respiratory system, Resistance
  - The part that is out of phase with the flow signal, called the *reactance* ( $X$ ), which represents the imaginary part of  $Z$ , and encompasses  $E$  and  $I$
- These real and imaginary parts are plotted against frequency
- Most clinical applications, the FOT is used to measure  $R$

# Principle

- An important disadvantage (unless an esophageal balloon is placed to measure transpulmonary pressure), the R measured is not of the lungs alone but of the entire respiratory system, thus including the upper airway and chest wall
- upper airway - markedly influence the measurement because of its high compliance and the propensity for glottis interference



**FIG. 10.9** (A) Mayo Clinic pulmonary physiology lab in the 1960s testing FOT using a loudspeaker and recorder. (B) A built-in loudspeaker generates an impulse of flow containing a wide range of frequencies (5 to 35 Hz).

(Courtesy CareFusion, Cardiopulmonary Diagnostics, Yorba Linda, CA.)