Assessment of Pediatric Lung Disease Using Multiple Breath Washout

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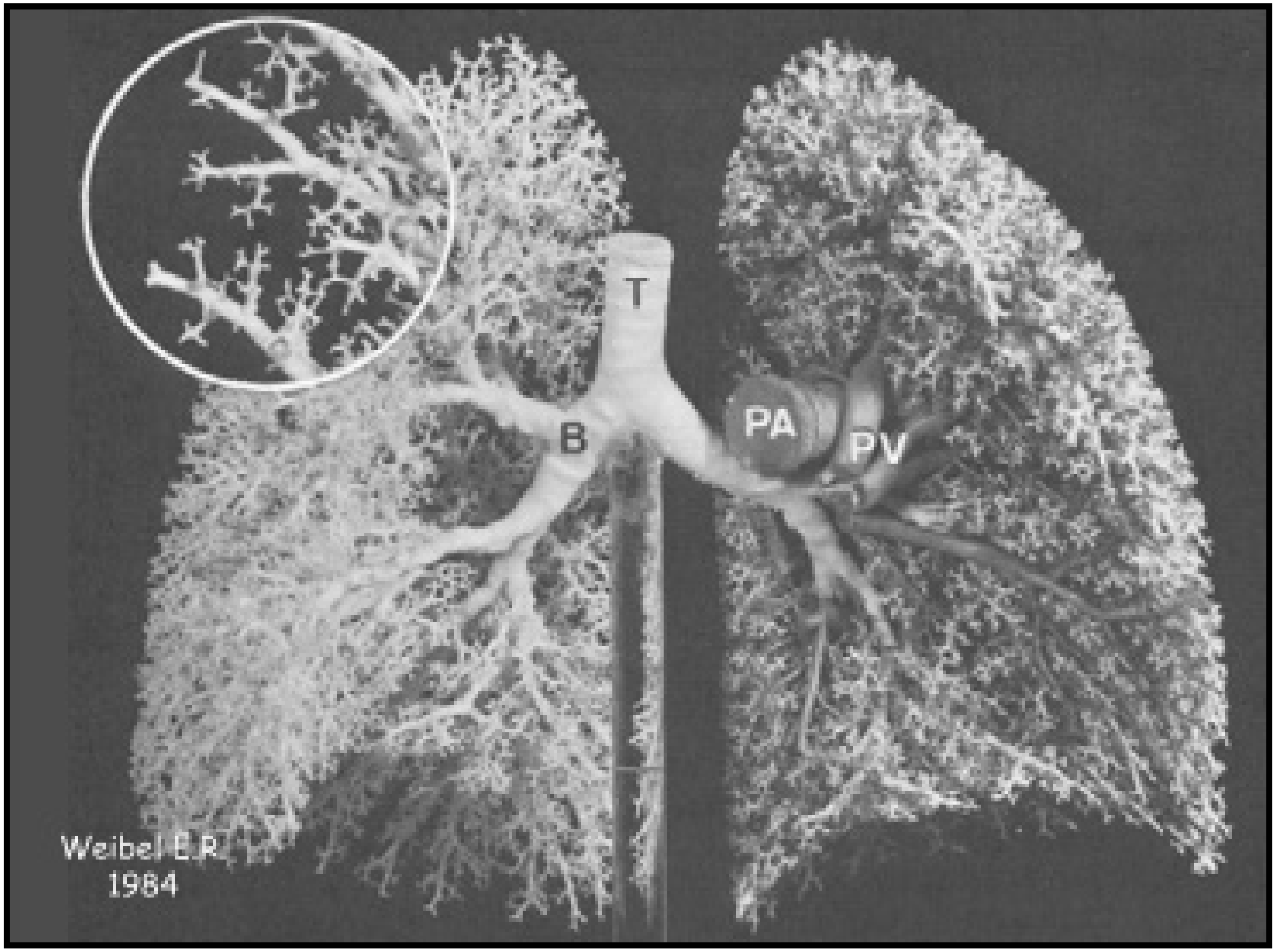
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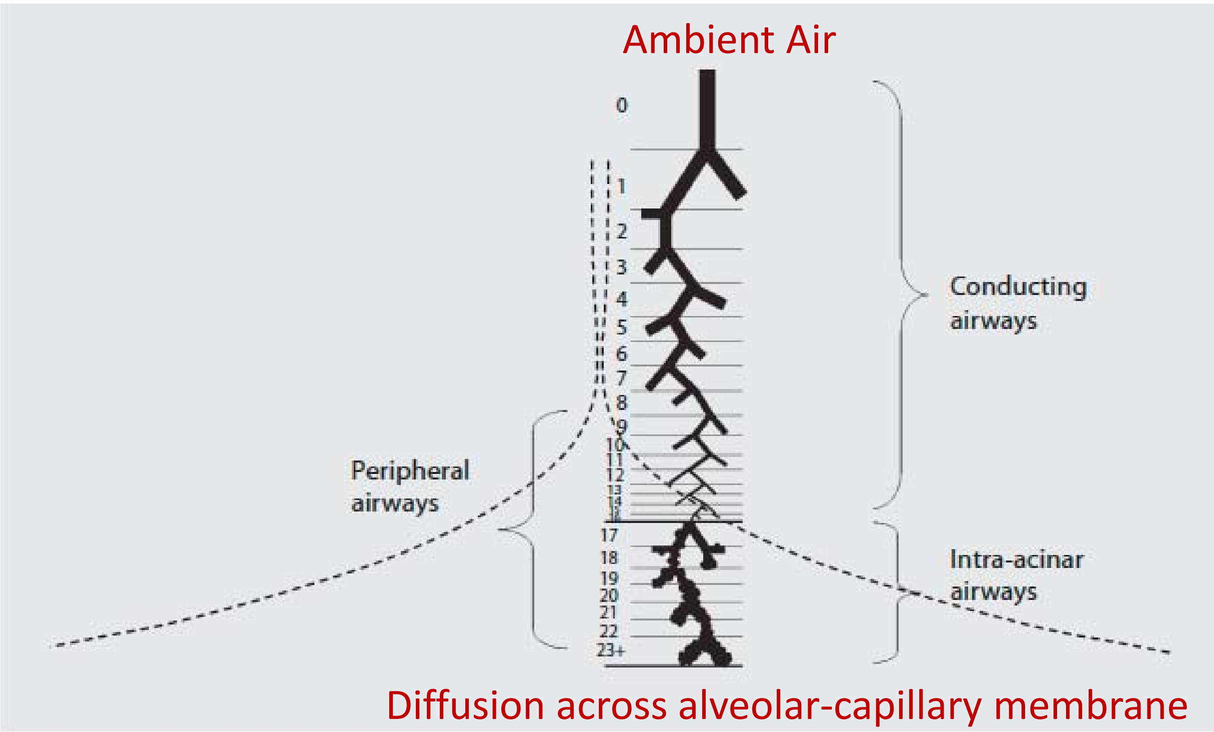
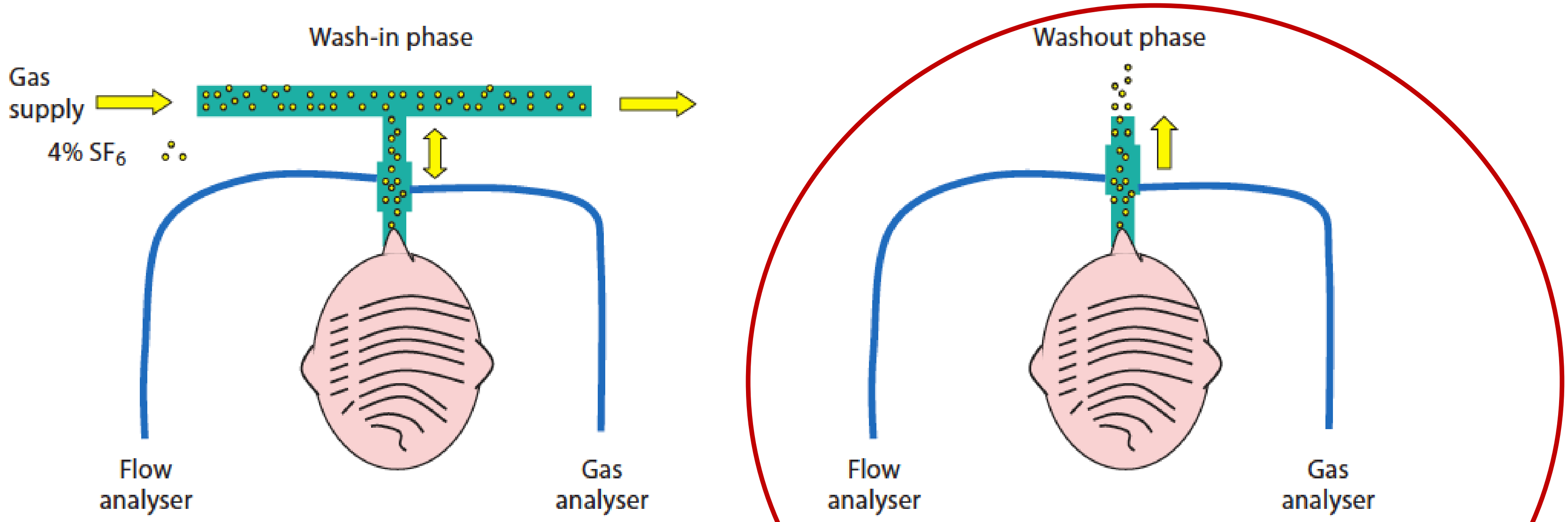
Gas Transport in the Lung



PD Robinson, et al. *Respiration* 2009;78:339–355

Multiple Breath Washout (MBW)

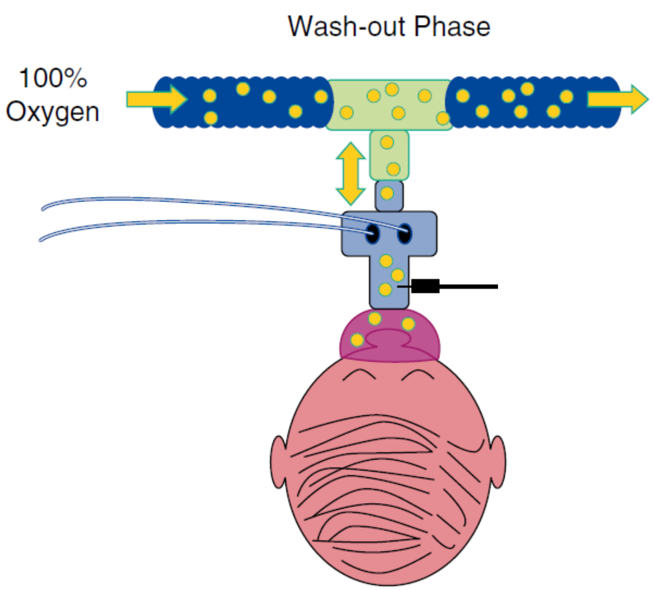
Tracer Gas Options:
- SF_6
- Helium

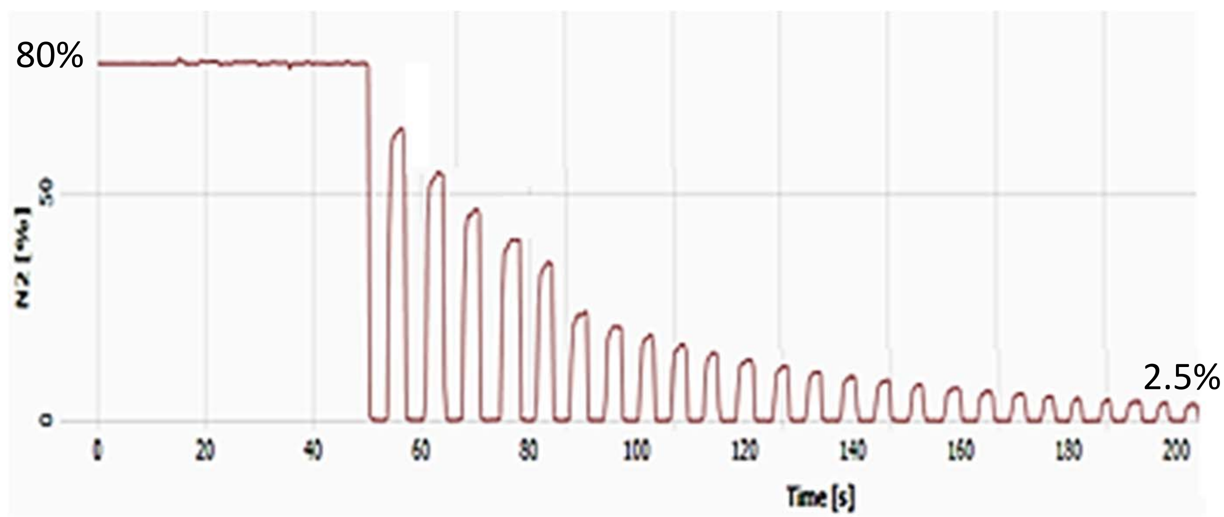


Measure concentration of tracer gas on exhalation

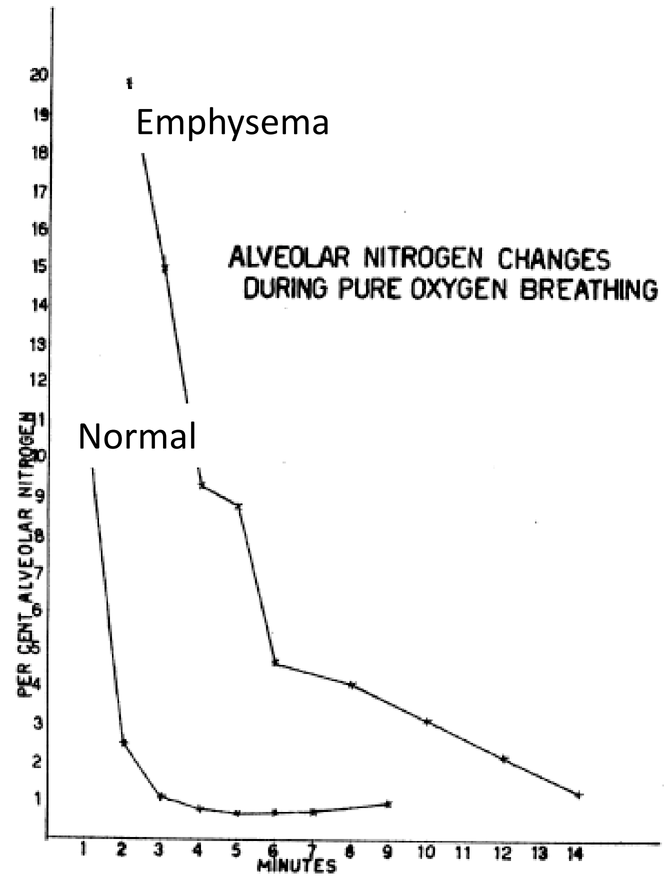
PD Robinson, et al. *Respiration* 2009;78:339–355

N_2 MBW Technique





Increased Washout Time Due to Impaired Ventilation



RC Darling, JCI 1940

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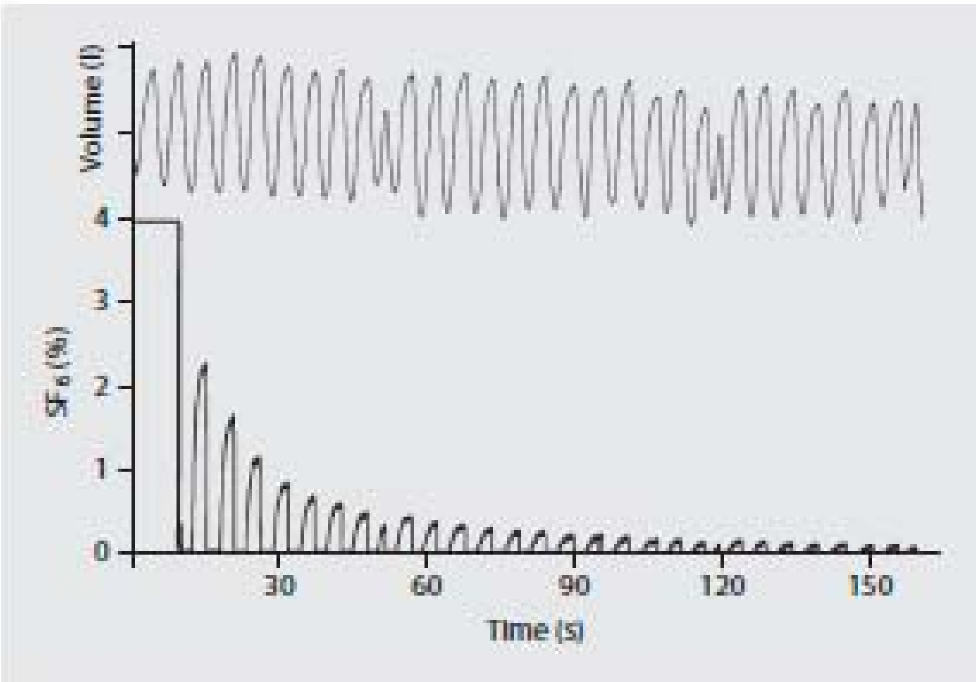
Lung Clearance Index (LCI)



PD Robinson, et al. *Respiration* 2009;78:339–355

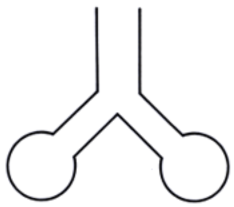
- LCI is the # of lung turnovers required to clear the lungs of tracer gas or N_2 to 1/40 original concentration (2.5%)

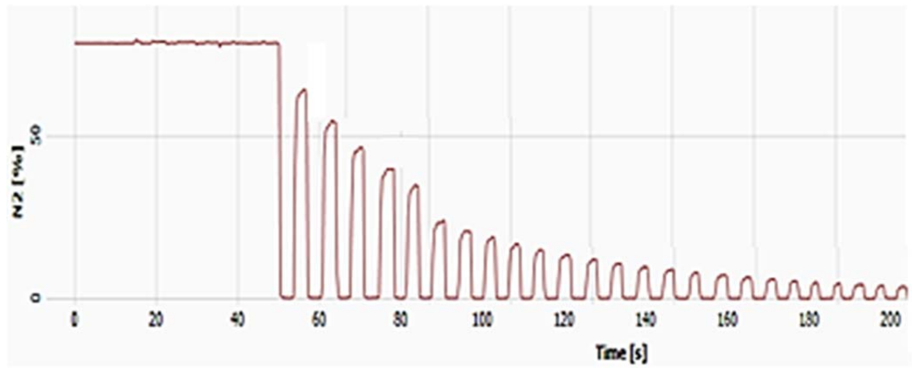
$$LCI = \frac{CEV\ (cumulative\ expired\ volume)}{FRC}$$

- LCI
  - Unitless
  - Normalized for lung size (don't need to adjust for height or weight)
- Higher LCI → More ventilation inhomogeneity

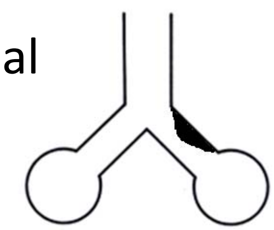
LCI: Normal vs Abnormal

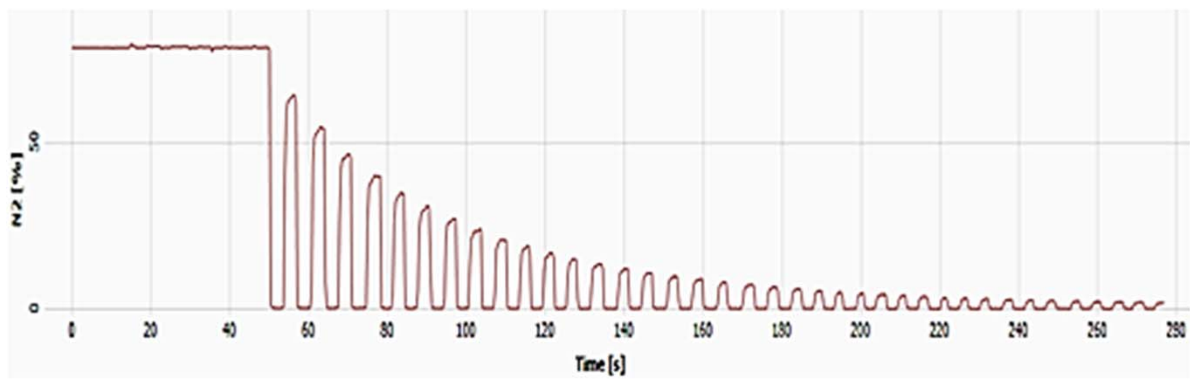
Normal





Abnormal





Multiple Breath Washout and the Lung Clearance Index

Respiratory and pulmonary N_2 clearance data for subjects with cardiorespiratory disease

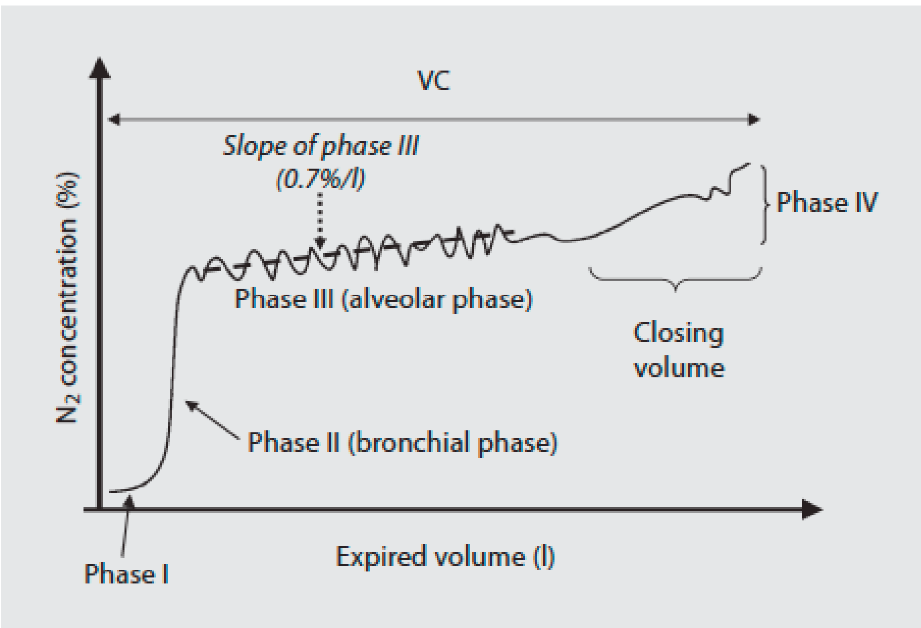
Subj.	Diagnosis	Sex	Age (*yrs.*)	Tidal vol. (*ml.*)	Resp. (*per min.*)	Ventilatory components						Average interval N_2 molecules remained				Pul. N_2 clearance delay (%)	FRC (*ml.*)	
						Phase 1		Phase 2		Phase 3		No. breaths		Minutes				
						f_1	w_1	f_2	w_2	f_3	w_3	Actual	Ideal	Actual	Ideal		Darling	ΣV_L
	Asthma																	
E. R.	mild	F	34	710	17	.46	.911	.54	.694	—	—	6.87	4.51	.41	.27	52	2,530	1,910
V. J.	mild	F	33	364	25	.71	.936	.29	.870	—	—	13.3	11.8	.53	.47	13	2,060	2,310
L. S.	moderate	M	16	525	22	.54	.979	.38	.950	.08	.722	33.5	17.2	1.5	.78	95	3,970	4,720
J. K.	severe	M	41	482	20	.53	.987	.47	.882	—	—	44.5	15.4	2.2	.77	190	3,250	3,750
	Emphysema																	
G. D.	moderate	M	70	437	17	.79	.980	.21	.844	—	—	40.7	18.9	2.4	1.1	115	4,600	4,370
N. R.	severe	M	58	312	22	.87	.990	.13	.820	—	—	87.5	27.8	4.0	1.3	215	4,680	3,710
J. C.	severe	M	59	395	20	.72	.991	.25	.926	.03	.622	83.4	24.4	4.2	1.2	240	4,670	4,600
W. A.	severe—asthma	M	60	497	16	.72	.981	.20	.862	.08	.603	39.7	11.4	2.6	0.74	248	3,880	3,440
S. F.	severe—asthma	M	66	467	19	.82	.981	.16	.858	.02	.418	44.5	16.7	2.3	0.88	166	4,250	4,180
	Congestive heart failure																	
J. P.	minimal	M	40	307	26	.86	.934	.14	.779	—	—	13.7	10.9	.53	.42	25	2,070	1,730
J. B.	moderate	M	39	574	13	.48	.953	.52	.771	—	—	12.5	6.67	.96	.52	89	2,400	2,170
G. B.	severe	F	39	451	30	.61	.847	.39	.626	—	—	5.0	3.90	.17	.13	29	1,580	1,030
E. W.	severe	F	36	320	32	.45	.972	.48	.926	.07	.752	23.4	14.7	.73	.46	60	2,330	2,700
G. W.	severe—with (?) silicosis	M	56	492	27	.78	.976	.22	.841	—	—	33.7	16.7	1.25	.62	102	4,570	5,560
B. T.	Bronchiectasis, L. lower lobectomy, 8 mos. pregnant	F	22	670	14	.17	.966	.75	.810	.08	.304	9.05	3.73	.65	.27	143	1,660	1,390
E. T.	Sarcoid-pulmonary cyst	F	26	400	31	.69	.973	.31	.850	—	—	27.6	14.3	.90	.46	93	3,330	2,640
T. C.	Pulmonary fibrosis	M	34	392	21	.48	.980	.47	.938	.05	.393	31.6	9.51	1.51	.45	233	2,620	2,760
L. W.	3 mos. post-pneumonectomy	M	65	430	23	.48	.961	.37	.892	.15	.635	16.1	7.75	.70	.34	108	1,850	1,750
A. G.	2 wks. post-pneumonectomy	M	54	556	24	.55	.952	.37	.885	.08	.498	14.5	7.40	.61	.31	97	2,700	2,040

WS Fowler, JCI 1952; 31: 40–50

Other MBW Measurements

- $LCI_{5.0}$ = Number of lung turnovers required to reach 1/20 (5%) of original concentration
  - Faster to measure that $LCI_{2.5}$
  - Easier for young children to perform
  - Less sensitive than $LCI_{2.5}$
- Normalized slope of phase III
  - S_{cond}: Convection dependent inhomogeneity
  - S_{acin}: Diffusion-convection interaction-dependent inhomogeneity
- Moment ratio analysis

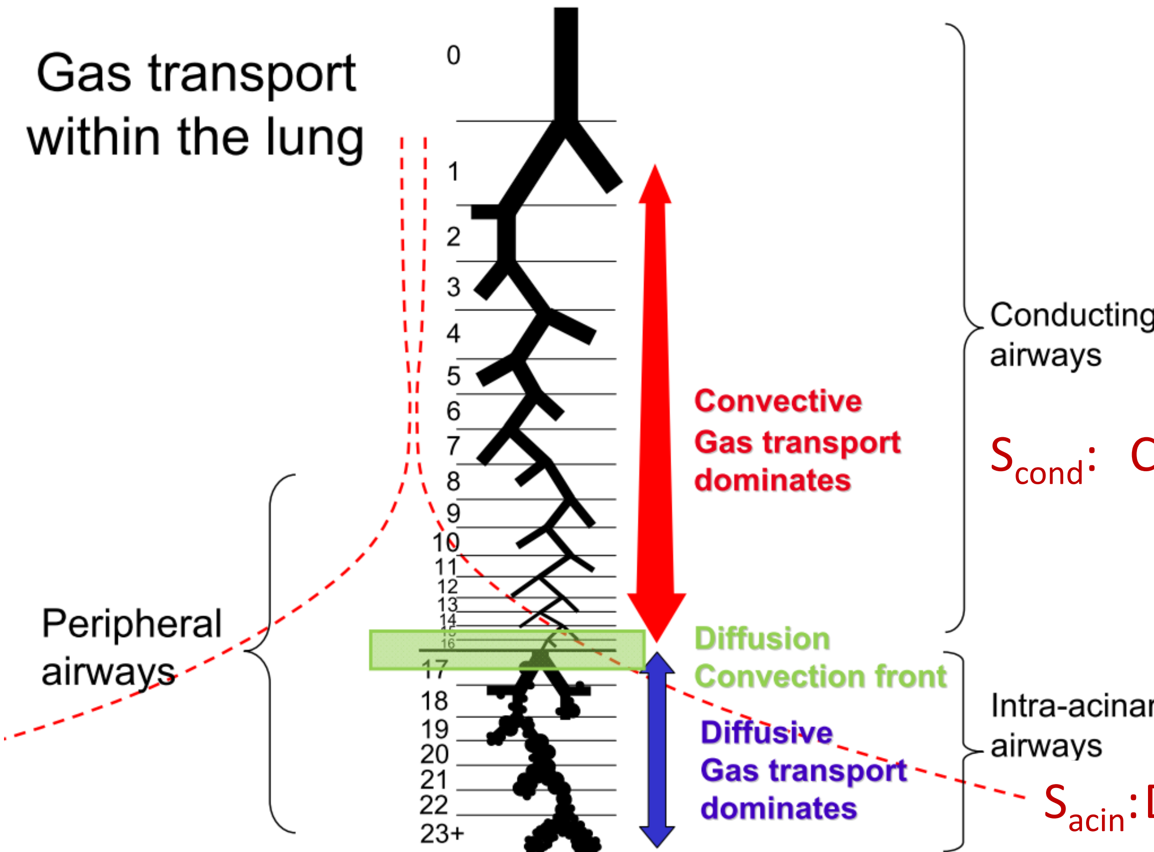
Normalized Slope of Phase III (SnIII)



- Phase III represents emptying of alveolar gas
- Phase III slope is calculated for each breath using linear regression
- Each breath is normalized for effect of washout gas
- SnIII=mean normalized phase III slope

PD Robinson, et al. *Respiration* 2009;78:339–355

S_{cond} and S_{acin}



S_{cond}: Convection dependent inhomogeneity

S_{acin}: Diffusion-convection interaction-dependent inhomogeneity

Paiva M Respiratory Physiology: an analytical approach 1989

Moment Ratios

- M0: The total area under the washout curve
- M1, M2, Mn…: Weighted values of the area segments under the curve
- ↑ M_1/M_0 or M_2/M_0 → ↑ Ventilation Inhomogeneity
- Moment ratios
  - Potentially more sensitive than LCI
  - More difficult to calculate
  - Role in clinical care and research requires further study

GM Saidel, et al. JAP 1975; S Stanojevic, et al. JCF 2015

MOMENTS

$$M_0 = \sum_{j=1}^{50} x_j$$

$$M_1 = \sum_{j=1}^{50} j \cdot x_j$$

$$M_2 = \sum_{j=1}^{50} j^2 \cdot x_j$$

$$j = 5\eta_j + 1$$

$$0 \le \eta_j < 10$$

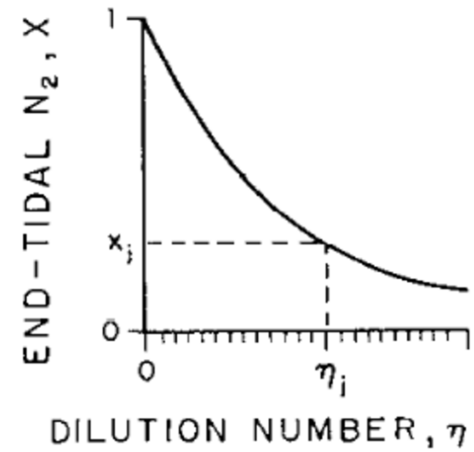


FIG. 2. Computation of moments.

Tracer Gas Selection

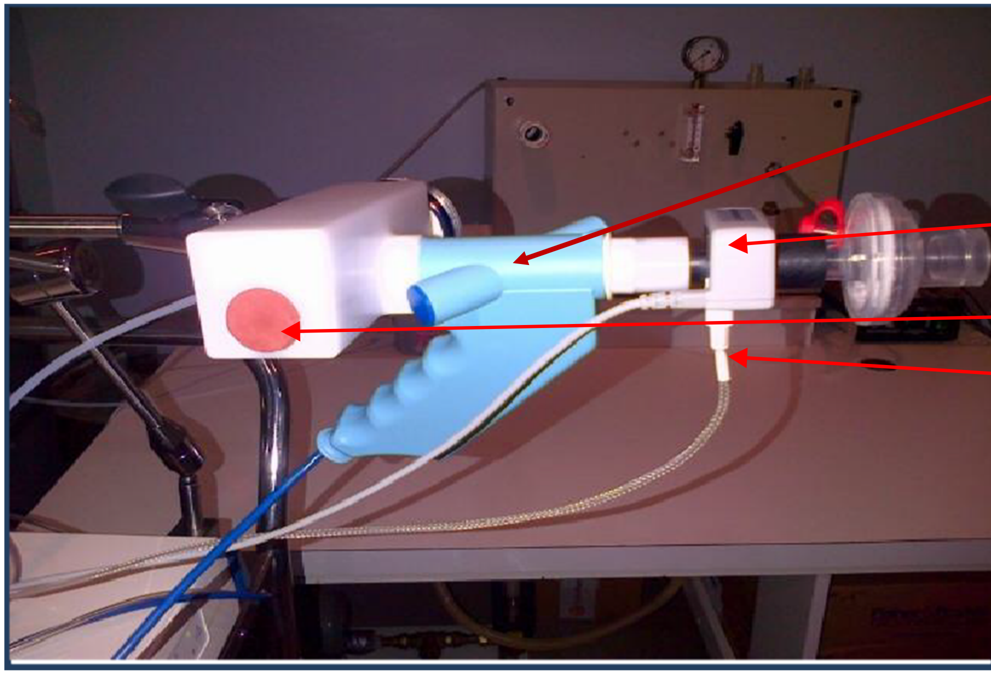
Tracer Gas	Comments
Sulfur Hexaflouride (SF_6)	• Traditionally requires mass spectrometer • Greenhouse gas→may require specialized ventilation
Helium	• Expensive • Difficult to obtain a He analyzer
Nitrogen	• Does not require wash-in period • Uses widely available gases • Potential for back diffusion of N_2 • N_2 analyzers are noisy and unreliable→Measured indirectly

MBW results vary depending upon gas selection and measurement system

MBW devices available in the USA

Device	Tracer gas	FDA Approved?	Comments
Eco-Medics Exhalyzer D	N2 washout	No	• Most widely used device in the USA • Raw data available for quality control • Option to use SF_6
Innocor LCI	SF_6	Yes	• Closed circuit: potential effect on breathing patterns • Limited data access for quality control
ndd EasyOne Pro	N2 washout	Yes	• Loud control valve • Limited data access for quality control

Eco-Medics Exhalyzer-D MBW Device



Flow sensor

CO_2 sensor

Connection to gas source

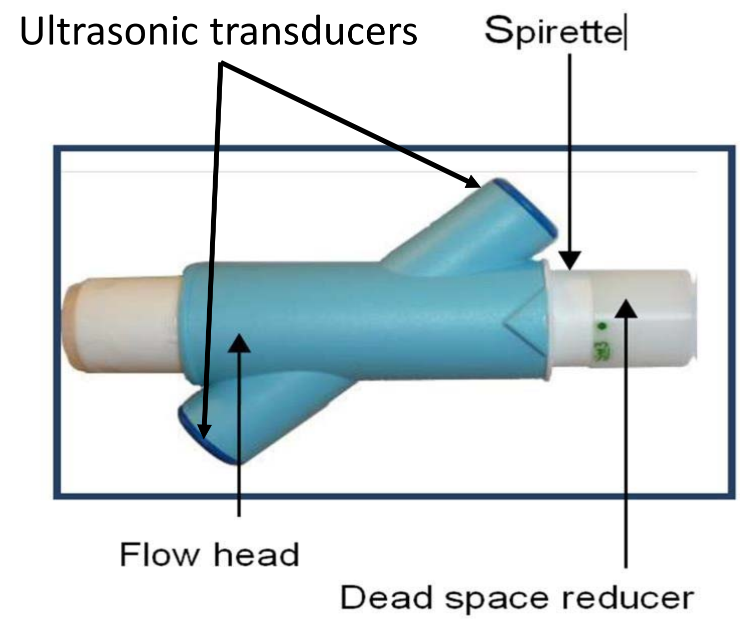
Sampling port for O_2 measurement

Flow, CO_2, and O_2 are measured at different points in the circuit: **Signals must be synchronized**

N_2 concentration=100% - (CO_2 conc + O_2 conc + correction factor)

Flow Sensor

- Gas composition is changing with each breath → Cannot use a mesh pneumotach
- Flow is measured by ultrasonic transducers

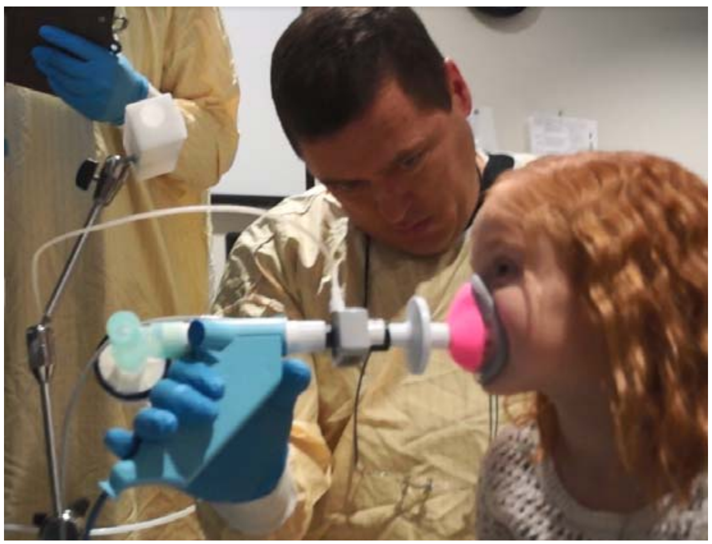


MBW Interface Choices

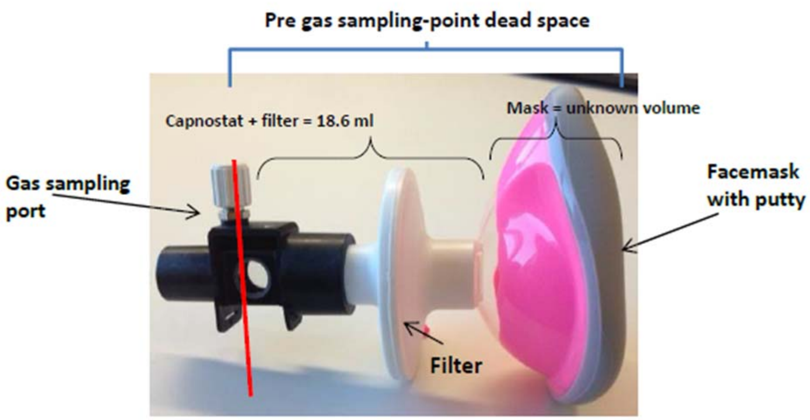
	Mouthpiece and Nose-Clip	Facemask
Distractions	Oral stimulation (e.g. chewing)	Avoids oral stimulation
Equipment Dead Space	Defined	Difficult to Define
Seal and Risk of Leak	Determined by subject	Operator determined
Impact of Nasal Airways	Removed	Unknown

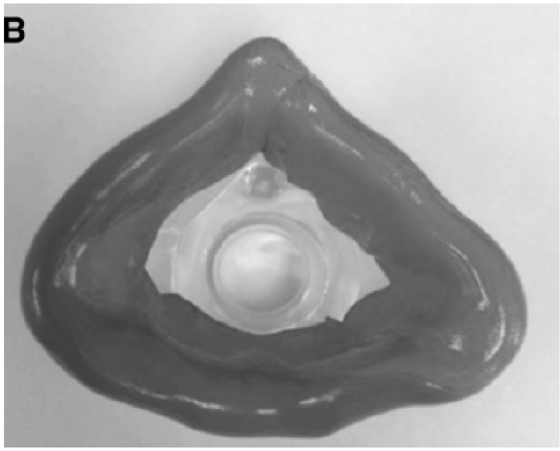
Robinson PD, AJRCCM 2018

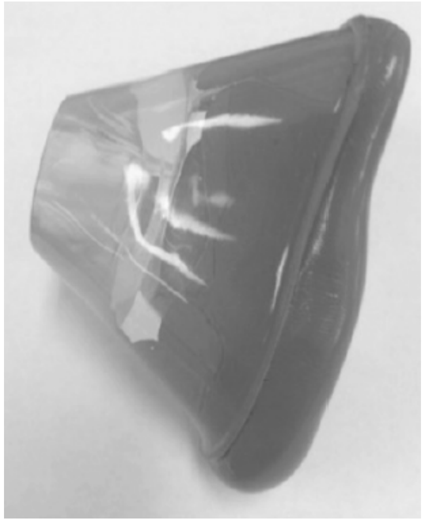
Face Mask vs. Mouthpiece for MBW in Young Children



Dead Space Reduction for Facemasks







PD Robinson, AJRCCM 2018

MBW Quality Control Criteria

- Steady tidal breathing
- No leak at mouthpiece or mask
- No laughing or coughing
- Flow, CO_2 , and O_2 signals are synchronized
- ≥3 breaths with concentration ≤1/40 of initial concentration
- 3 reproducible maneuvers (values within 10% of each other)

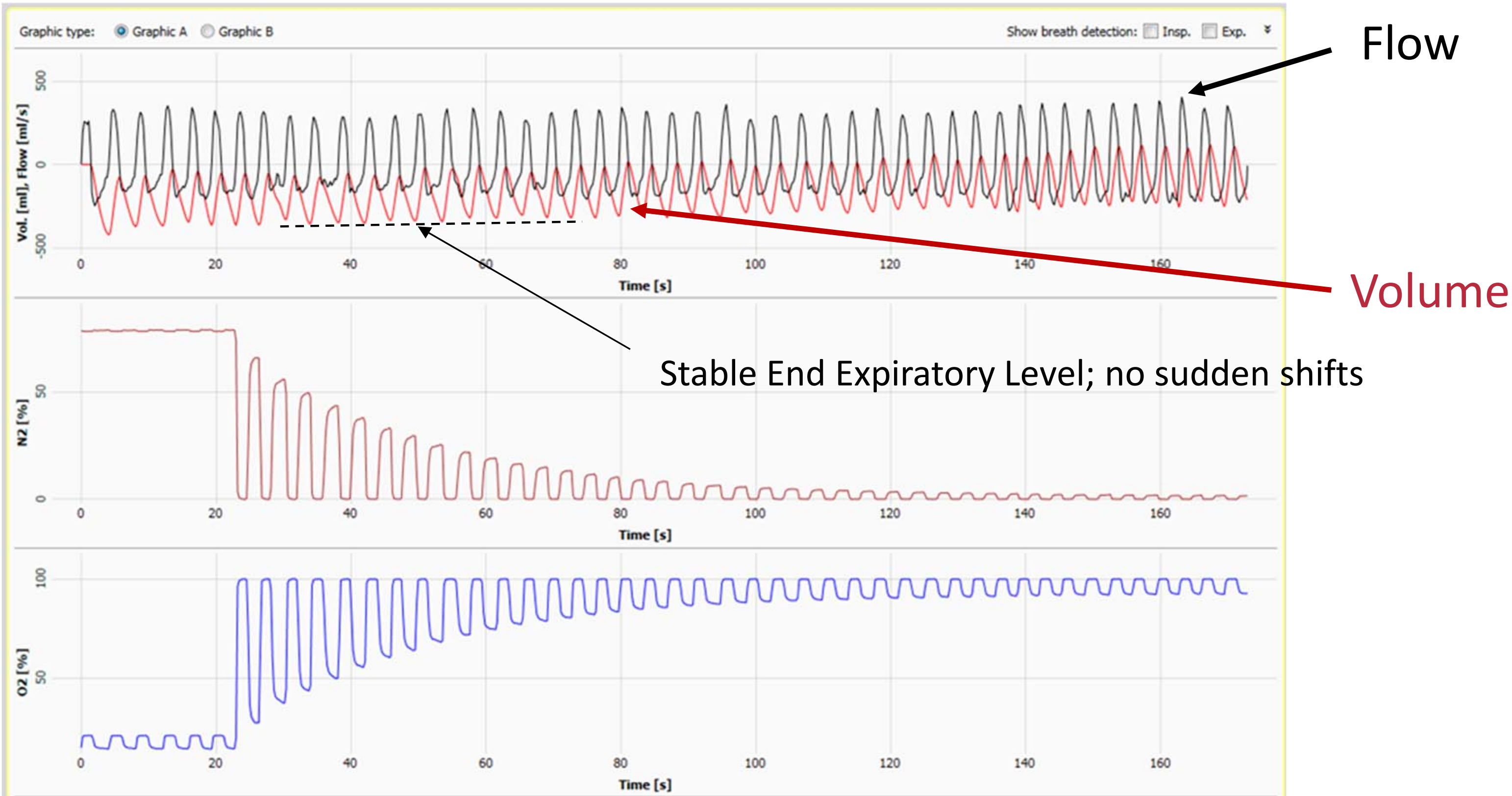
PD Robinson, et al. ERJ 2013; PD Robinson, et al. AJRCCM 2018

MBW Quality Control: Training is Key!

- **Careful, rigorous training is KEY**
- Site certification with age-appropriate subjects
- Ongoing QC
- Standardized equipment

Robinson PD, AJRCCM 2018

Acceptable MBW



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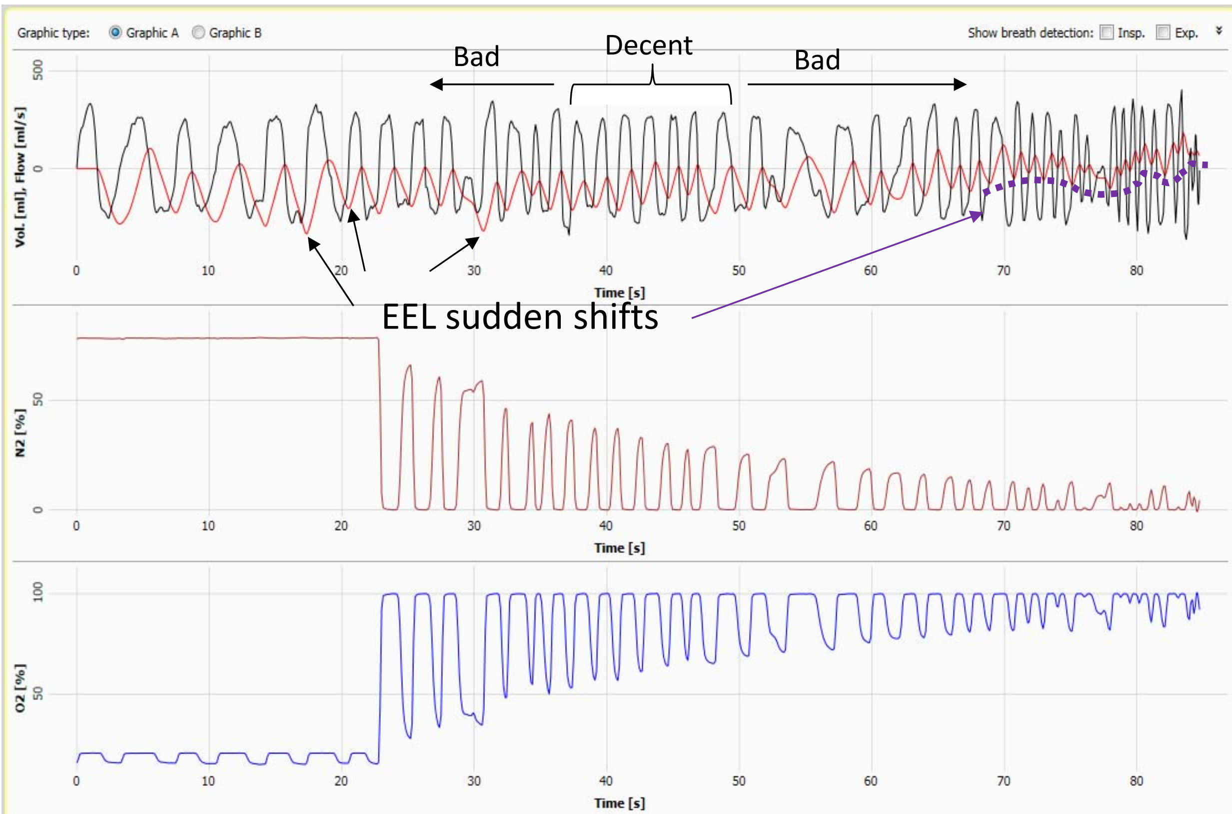
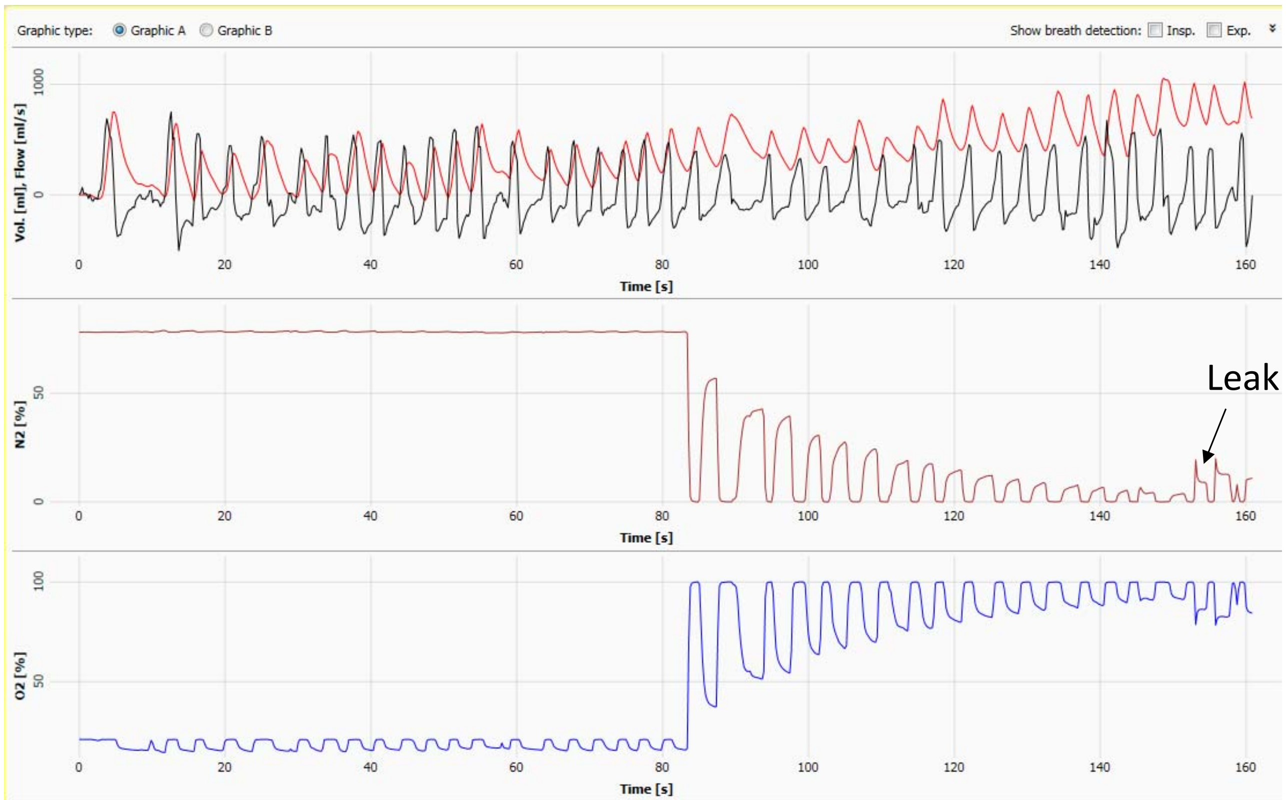
Unacceptable MBW: Shifting EEL

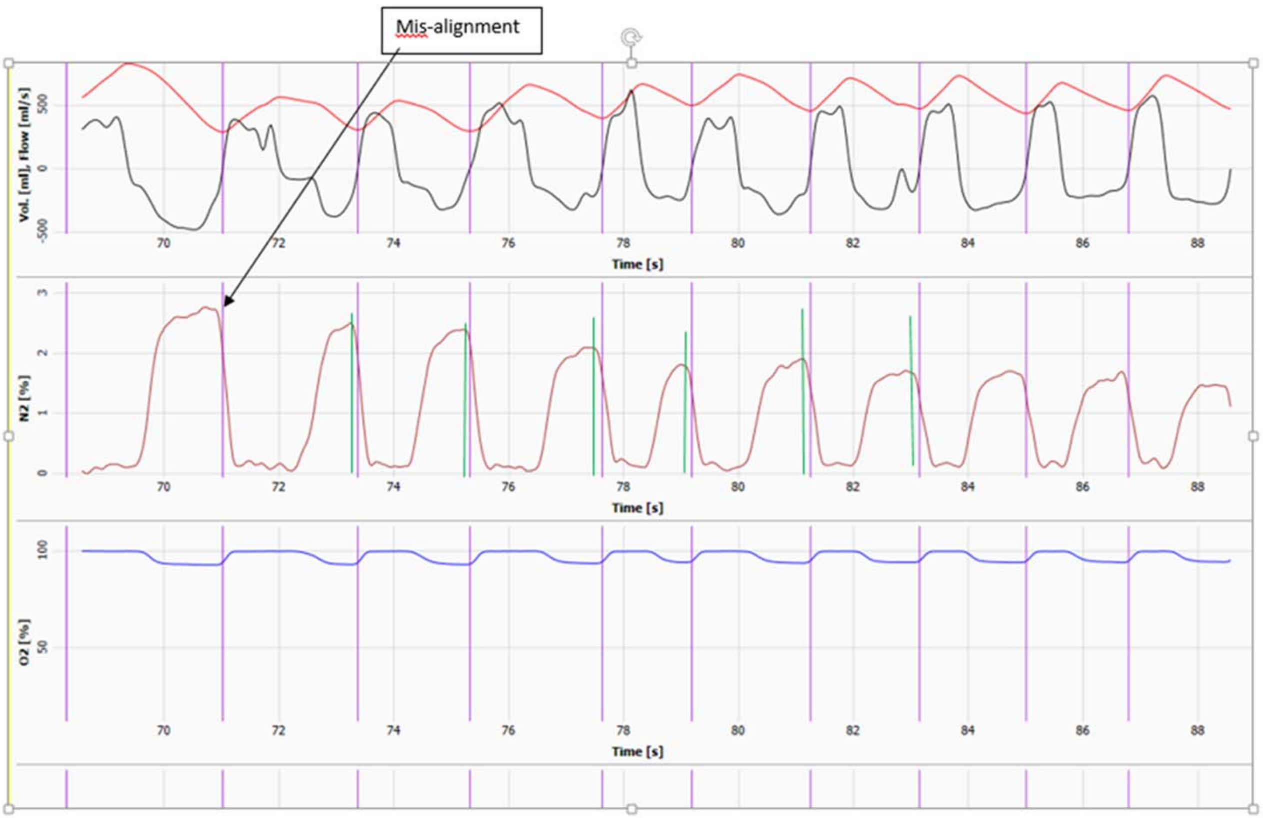


Shifting EEL = Shifting FRC

Unacceptable MBW: Leak



Acceptable MBW: Unsynchronized Signals



The Black arrow illustrates mis-alignment. The green lines represents what would be a more appropriate alignment.

Signals can be manually synchronized after the test

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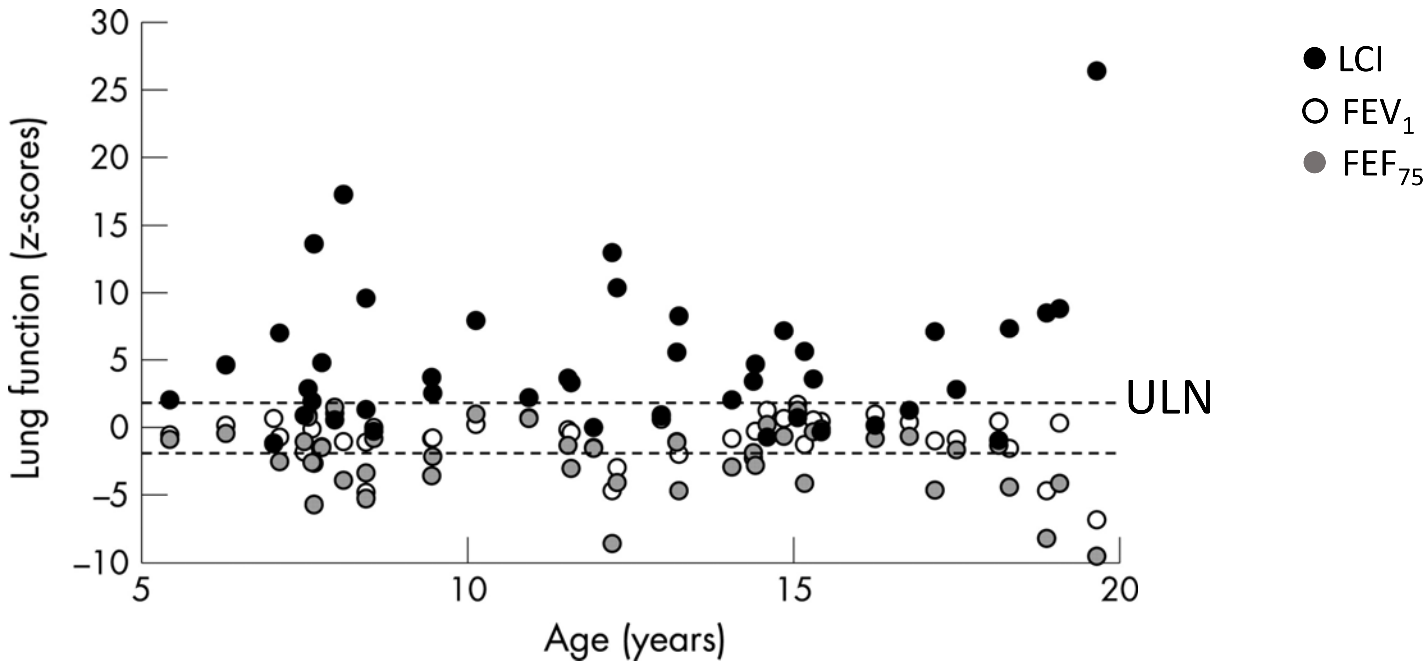
Challenges and Limitations of Infant MBW

- Tracer gas challenges
  - SF_6: Needs mass spectrometer
  - N_2 washout: O_2 affects breathing pattern
    - Can potentially overcome this by prebreathing at 30% FiO_2
- Dead space issues
- Requires sedation
- Infants have small tidal volumes and low flows → small errors in synchronization or delays in response time can lead to large measurement errors
- **Infant MBW remains a highly technically challenging research technique at this time**

MBW in Cystic Fibrosis

LCI in Children with Cystic Fibrosis



65% of children with normal FEV1 had an abnormal LCI

PM Gustafsson, et al Thorax 2008

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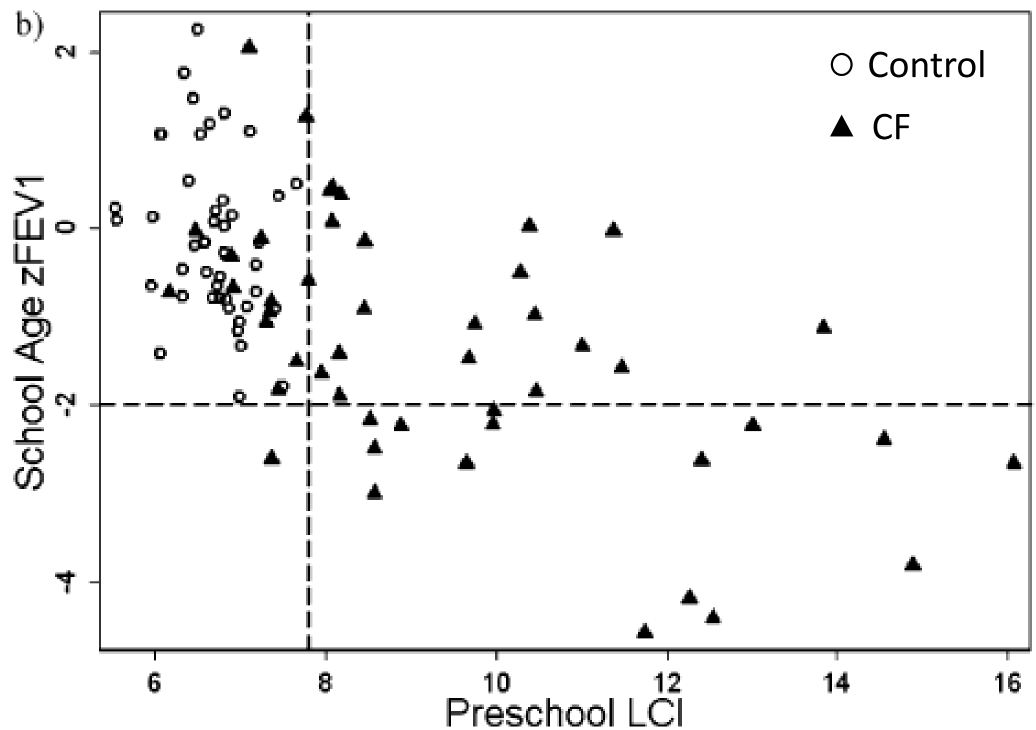
Preschool LCI Predicts School Age FEV1



P Aurora, et al. AJRCCM 2011

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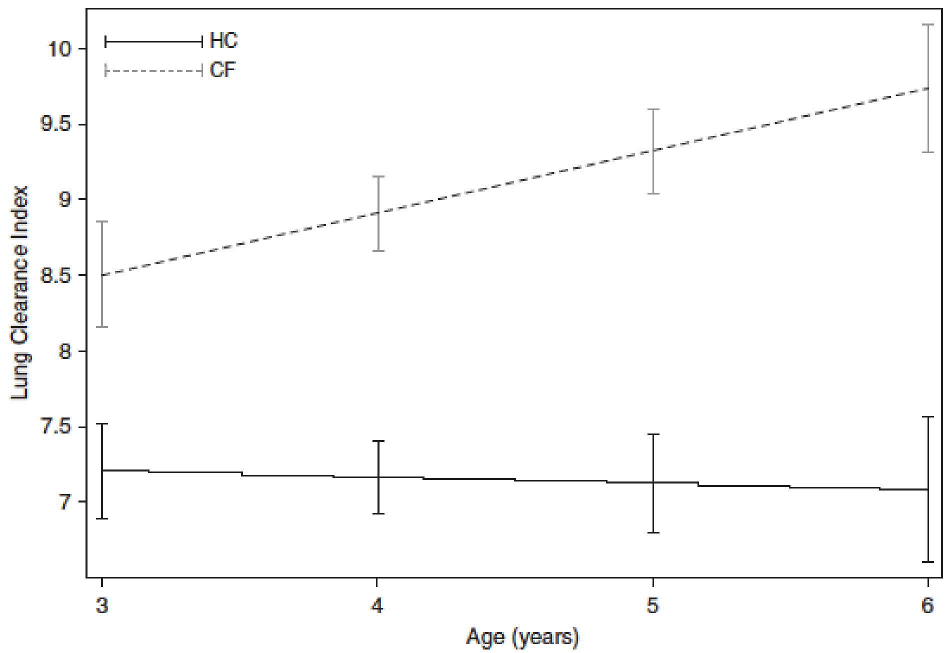
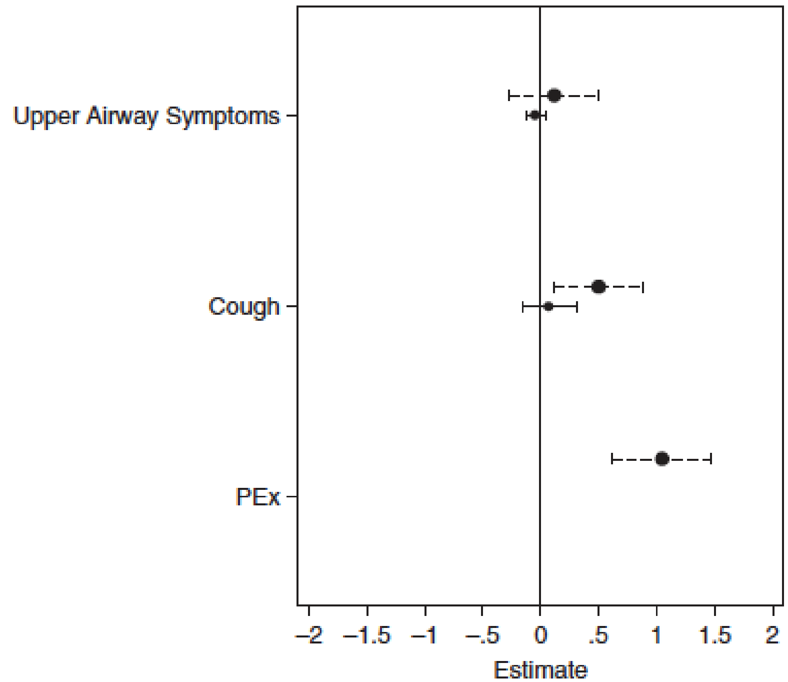
LCI in Preschoolers with CF





S Stanojevic, et al. AJRCCM 2017

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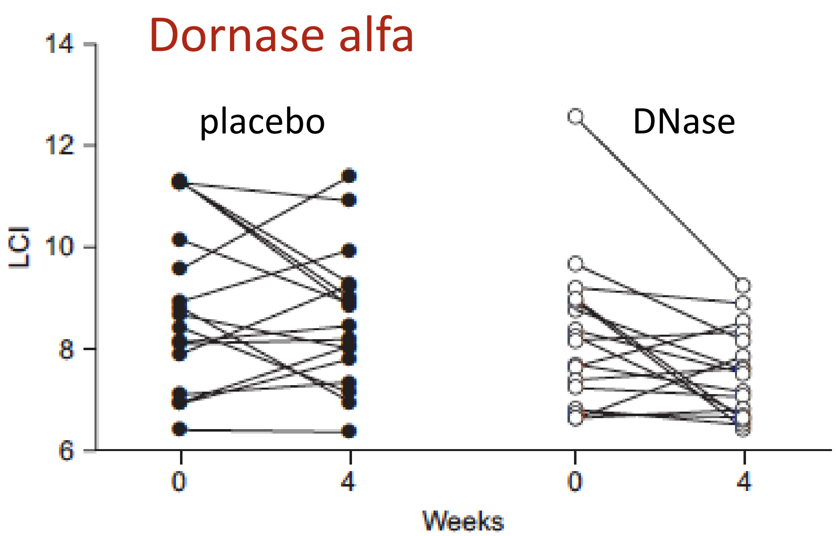
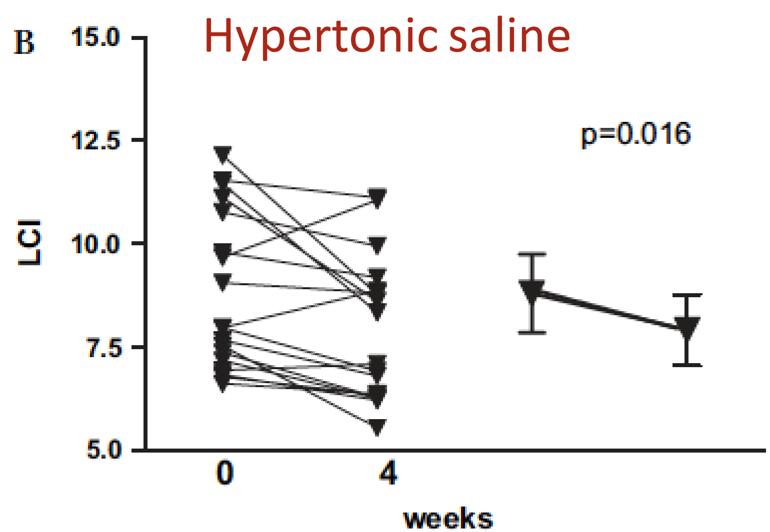
Hypertonic Saline and DNase Lower LCI in CF





R Amin, et al. Thorax 2010; R Amin, et al ERJ 2011

MBW in CF: Other Studies

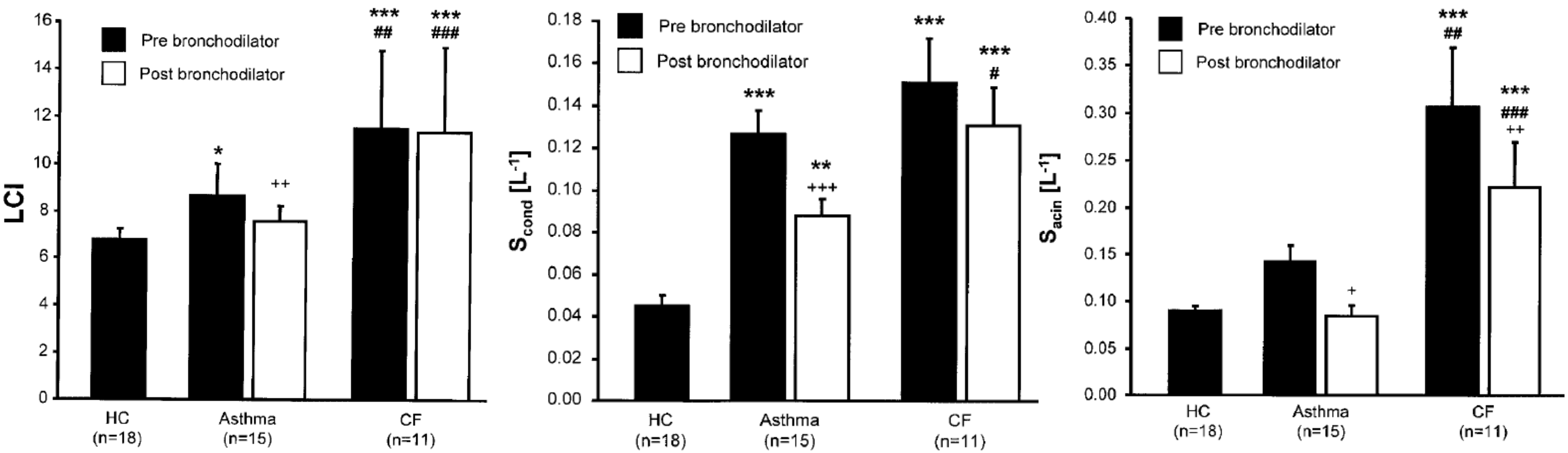
- LCI improves in response to other CF therapies
  - Ivacaftor
  - Hypertonic saline in infants and preschoolers
- LCI correlates with
  - Bronchiectasis seen on chest CT
  - Infection and inflammation
- Variable changes in LCI after treatment of pulmonary exacerbation
  - Potential for treatment to open up poorly ventilated units

LCI in Asthma

	Controls	Asthma	P value
Mean (SD) FEV_1 z-score	−0.69 (0.88)	−1.09 (1.28)	0.16
Range	−2.64–1.28	−4.00–1.82	
Mean (SD) LCI (CEV/FRC)	6.24 (0.47)	6.69 (0.91)	0.02
Range	5.14–7.05	5.49–9.46	
Mean (SD) S_{cond}, Vt corrected	0.017 (0.02)	0.026 (0.02)	0.06
Range	−0.03–0.06	−0.01–0.09	
Mean (SD) S_{acin}, Vt corrected	0.12 (0.06)	0.14 (0.02)	0.23
Range	0.02–0.29	0.05–0.40	
Mean (SD) Vt (l)	0.55 (0.24)	0.45 (0.17)	0.07
Range	0.19–0.99	0.23–0.80	
Mean (SD) FRC (l)	2.14 (1.02)	1.91 (0.78)	0.31
Range	0.80–4.51	0.85–3.82	

KA Macleod, Thorax 2009

MBW in Asthma vs CF



PM Gustafsson. Pediatr Pulmonol. 2007; 42:168–176

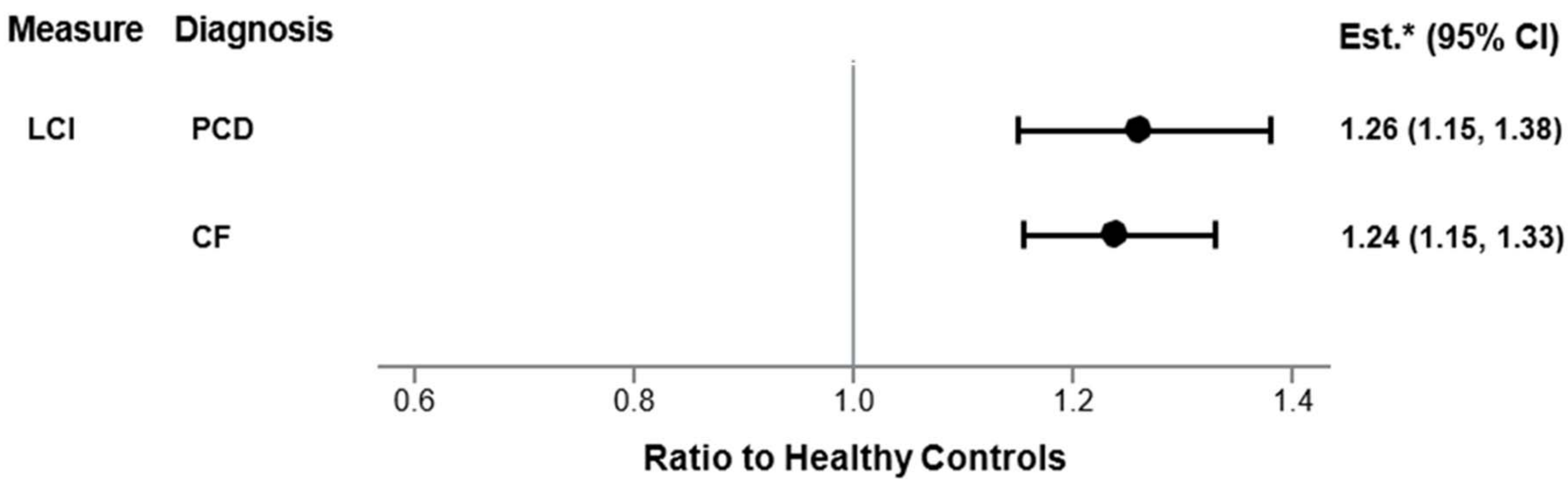
LCI in PCD

	HCs (n=70)	PCD (n=38)
FEV1 z-score	0.15 (−0.46 to 0.64)	−1.54 (−2.1 to −0.43)
FEV1/FVC z-score	−0.16 (−0.91 to 0.40)	−1.52 (−2.20 to −1.01)
FEF25–75 z-score	−0.39 (−0.91 to 0.42)	−1.99 (−2.68 to −0.61)
LCI	7.1 (6.7 to 7.5)	9.48 (8.28 to 10.92)
LCI z-score	0.17 (−0.54 to 0.67)	3.58 (1.84 to 5.70)

47% of patient with normal FEV1 had an abnormal LCI

M Boon et al; Thorax 2015

LCI in PCD and CF



* Represents ratio of geometric means, using exponentiated parameter estimates from log-transformed data

- LCI was abnormal in 21/36 (58%) CF patients and 11/18 (61%) PCD patients
- FEV_1 was abnormal in 5/36 (14%) CF patients and 2/18 (11%) PCD patients.

B Kinghorn, et al. Ann ATS 2020

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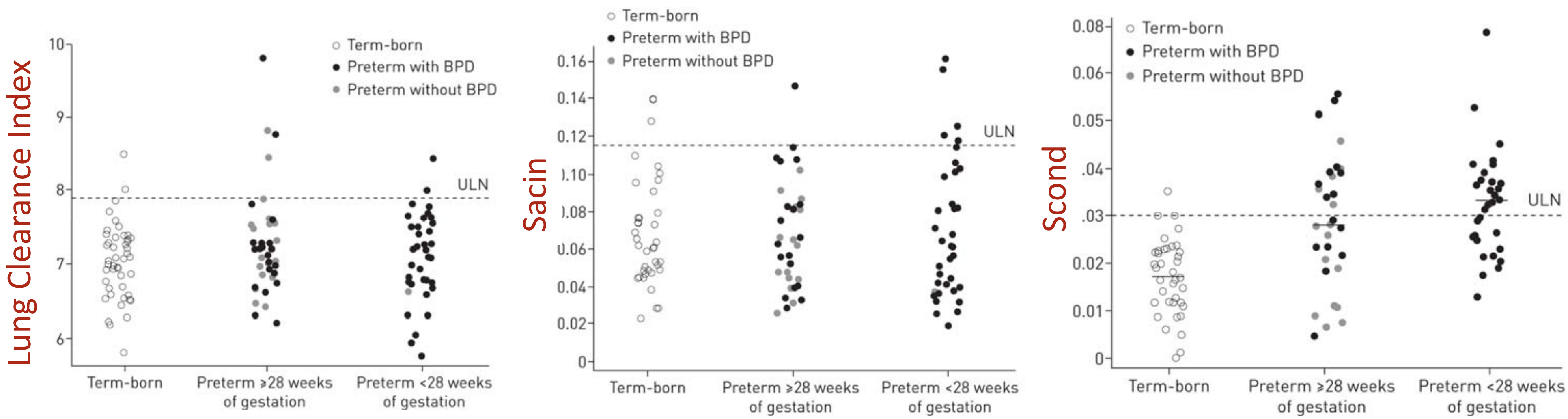
MBW in Preterm Children



- Children 6-16 y/o
- GA<37 w
- No difference in LCI and Sacin
- Scond significantly higher in preterm

S Yammine, et al. ERJ 2016

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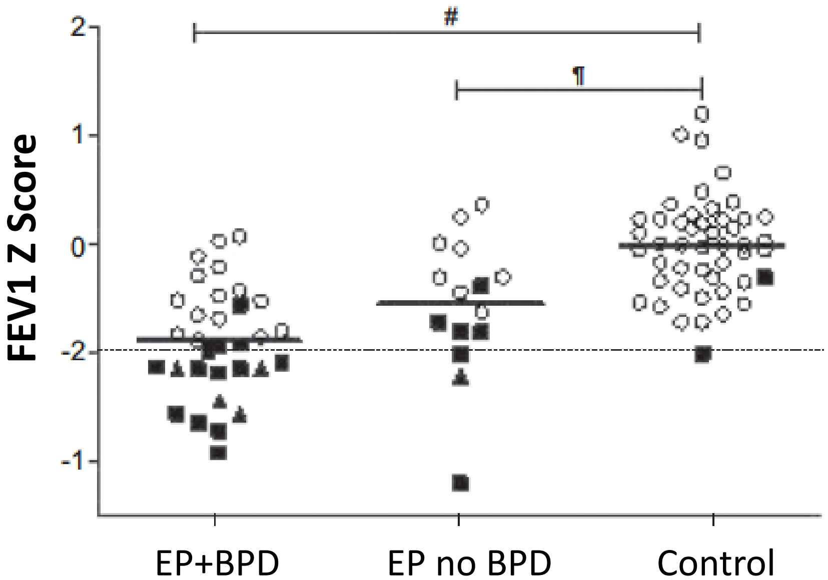
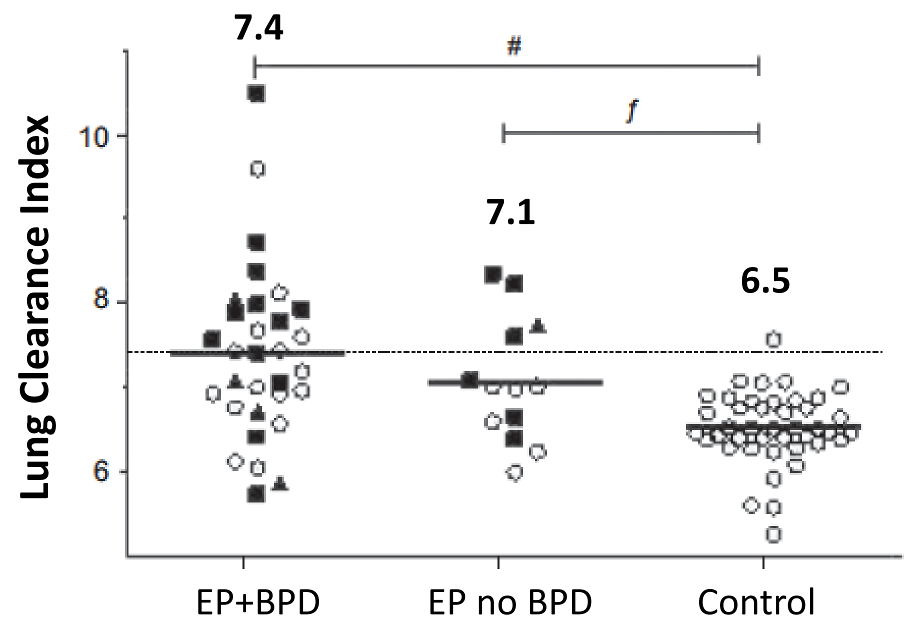
LCI in Extremely Preterm Children





- GA<26 weeks
- 49 children tested at 11 years old

S Lum, ERJ 2011

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LCI in Pediatric Lung Diseases

	Relative increase in LCI
CF	↑↑↑
PCD	↑↑↑
Asthma	↑
BPD	↑

Application of MBW to Research and Clinical Care

- Research
  - Most useful for CF and PCD
  - Study populations
    - Young children
    - Mild disease
  - Infant MBW is very challenging
- Limitations/challenges for clinical use
  - Time
  - Billing
  - Technical expertise
  - MCID is still not well defined

MBW Summary

- MBW is a sensitive measure of ventilation inhomogeneity and airway disease
- Lung clearance index (LCI) is the most common MBW measurement
  - Other measurements are available
- Rigorous training and attention to detail required for high quality data
- MBW has great potential as a research tool in mild and early CF lung disease