Lung clearance index in evaluating young children with lung disease

Dario Prais MD
Pulmonary Institute
Schneider Children's Medical Center of Israel

Multiple Breath Washout (MBW)

- Multiple breath *inert gas* washout
- A gas dilution technique
- Used to assess ventilation distribution and measure FRC
- Indicator of small airway disease (m/p)

Multiple-breath washout (MBW)

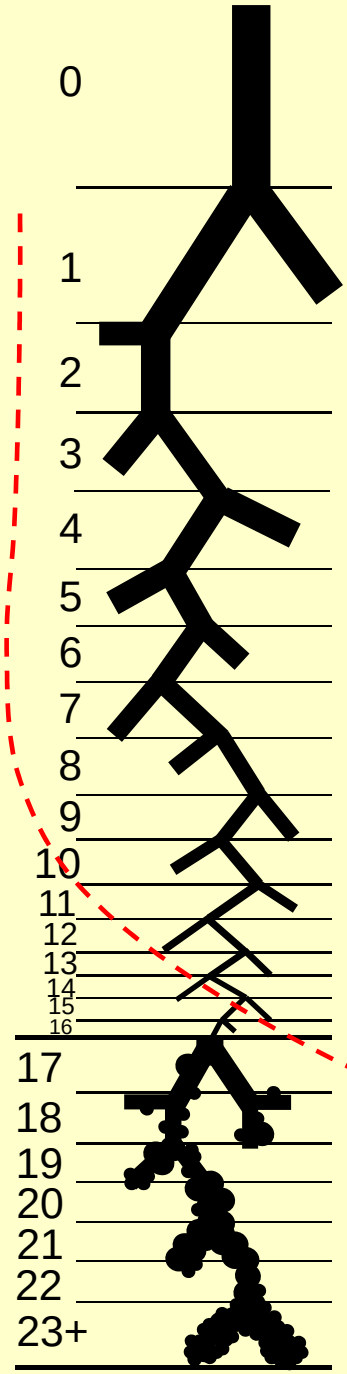
- Why?
- How?
- What for?

Conventional measurements

- Spirometry
  - ✓May be insensitive for assessing peripheral airway disease
  - ✓Often normal in the early stages of disease
  - ✓Age dependent
- Peripheral airways contribute little to overall resistance

Fuchs, Paeditr Respir Rev, 2011

Peripheral airways contribute little to overall resistance



Adapted from P Aurora, ERS, 2007

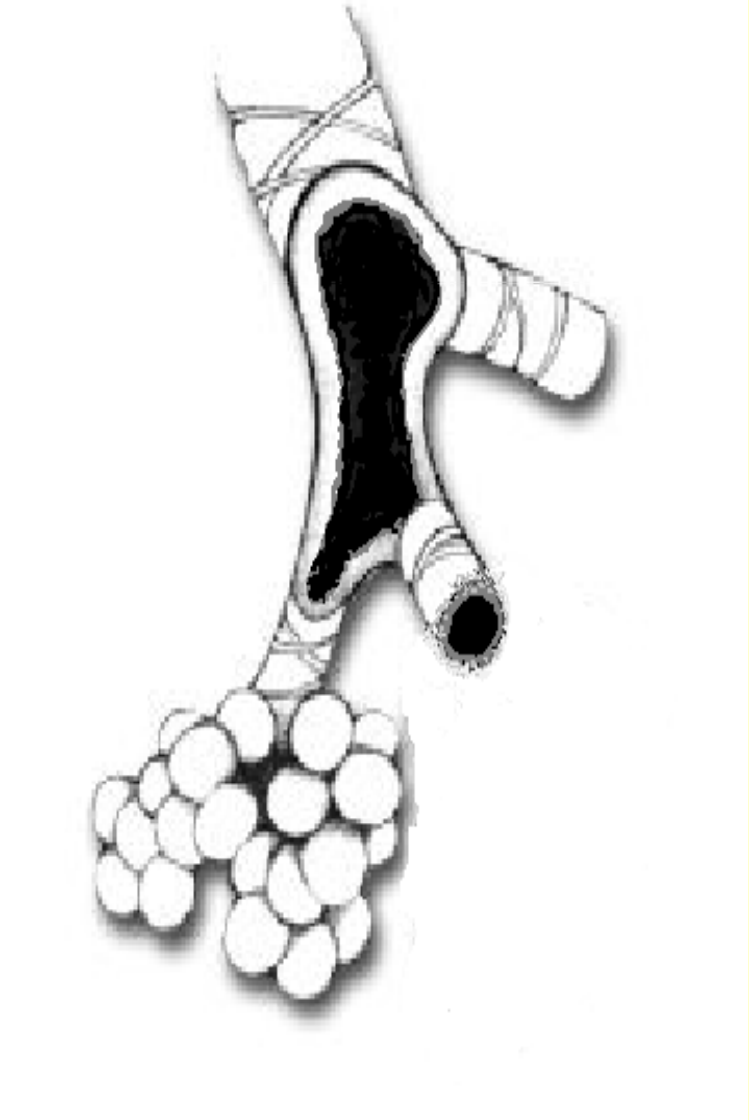
Conducting airways

Peripheral "small" airways

Intra-acinar airways, gas exchange zone

Healthy peripheral airway

Adapted from P Aurora, ERS, 2007

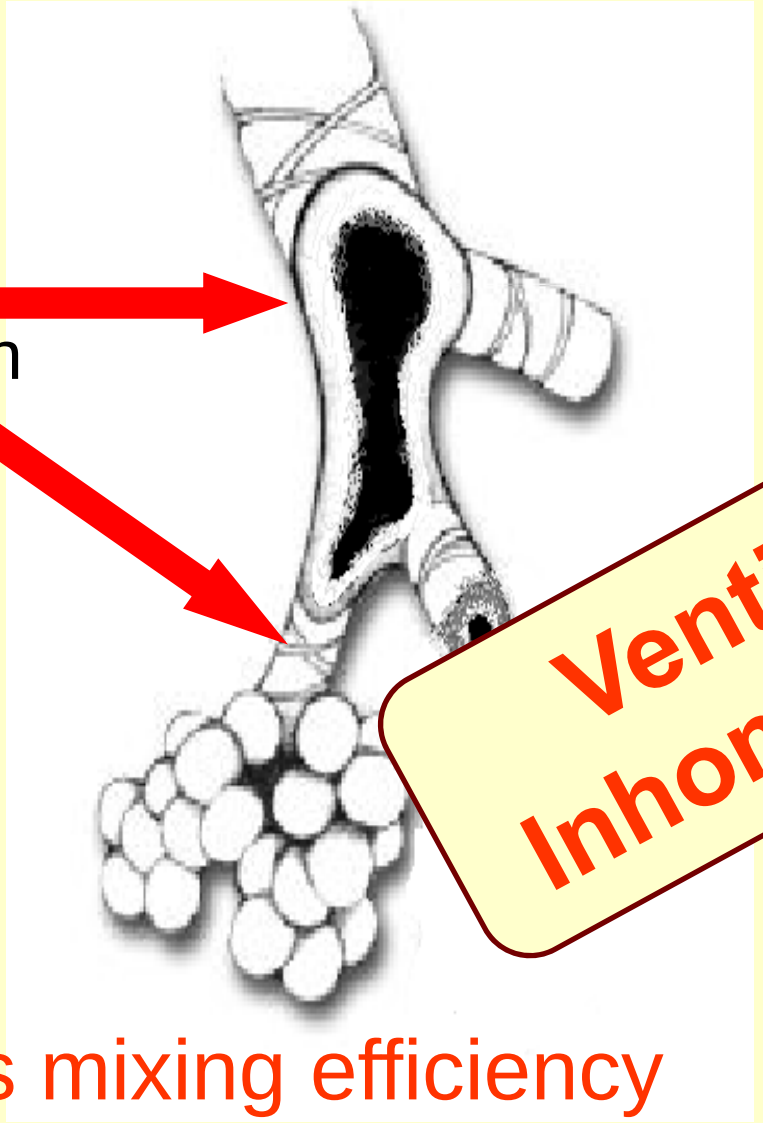


Peripheral airway in CF

Adapted from P Aurora, ERS, 2007

Obstruction

- smooth muscle contraction
- mucus collection
- airway wall thickening



Ventilation Inhomogeneity

- Gas trapping
- Reduced gas mixing efficiency

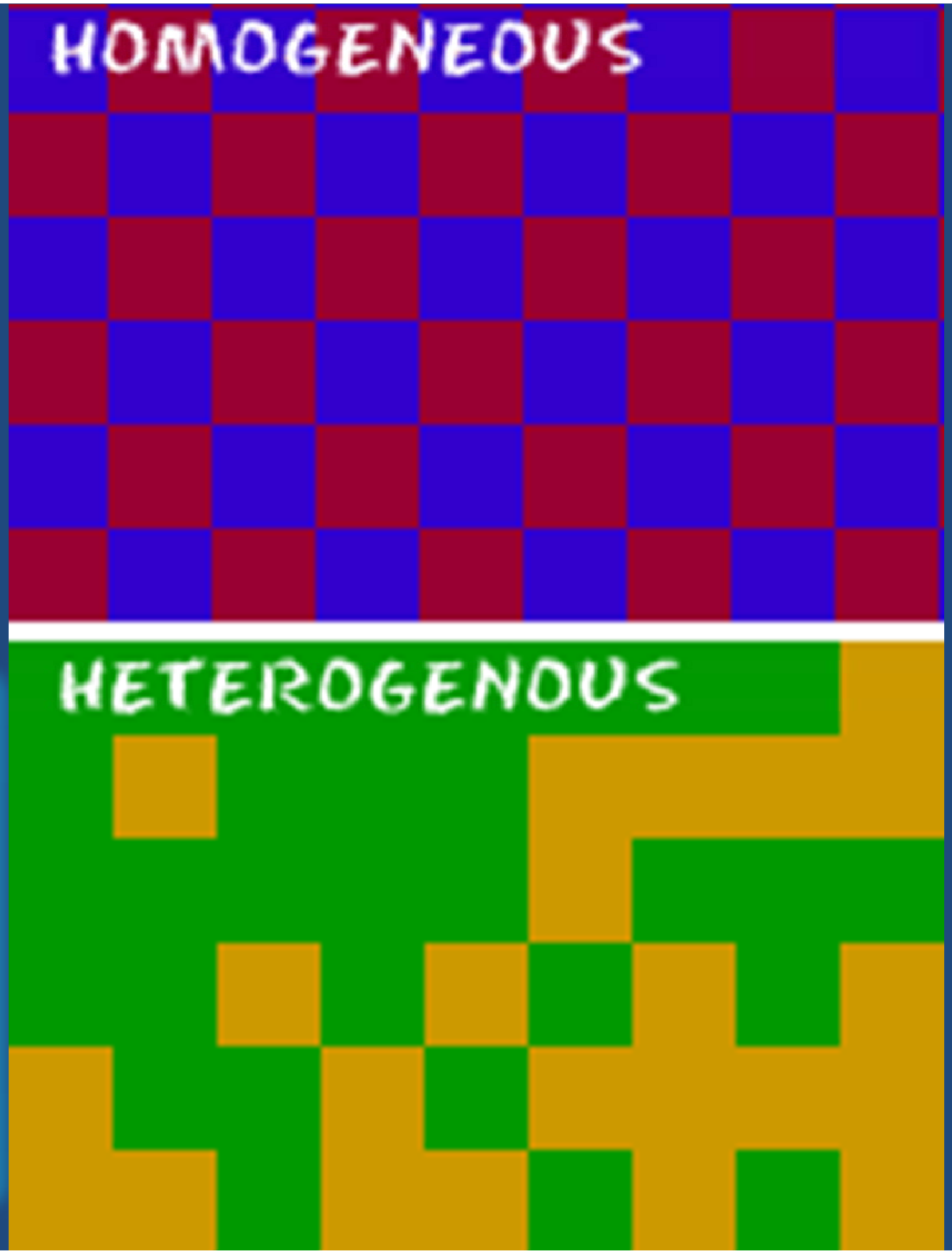
Ventilation inhomogeneity

- Changes in small airways lead to inhomogeneous ventilation of different parallel airways.
- Inhomogeneous emptying of peripheral lung units.

- Ventilation inhomogeneity (VI)
  - ✓ Delayed clearance of tracer gas during MBW.

Fuchs, Paeditr Respir Rev, 2011

Non-uniform ventilation distribution



MBW methodology

- Gas dilution techniques assessing ventilation distribution
- Regular tidal breathing (minimal cooperation)
  - ✓ Potentially applicable in any age.

- Tracer gas:
  - ✓ Wash-in: inert tracer gas (SF_6, He, Ar) inspired until equilibrium → washout by breathing room air.
  - ✓ Resident nitrogen (N_2) washed out while inspiring 100% oxygen

- Measurement of flow and gas concentration

Fuchs, Paeditr Respir Rev, 2011

Lung clearance index (LCI)

- LCI – parameter used to describe ventilation inhomogeneity (VI)

LCI is the number of volumes (FRC) that the subject tested needs to turnover (i.e. breath) to clear the lungs from the marker gas.

Fuchs, Paeditr Respir Rev, 2011

Lung clearance index (LCI)

- LCI is the number of volumes (FRC) that the subject tested needs to turnover (i.e. breath) to clear the lungs from the marker gas.
- defined as the number of times the lung volume has to be "turned over" to clear the lungs from an inert tracer gas (or nitrogen).

Lung clearance index

$$LCI = \frac{\text{Cumulative expired volume}}{\text{Required to washout a tracer to 1/40 of stating concentration}}$$

$$\text{FRC}$$

= Number to lung turnovers to washout the tracer gas

Lung clearance index (LCI)

Number to lung turnovers to washout the tracer gas

- In a healthy person, about 5 to 7 "turn-overs"

BUT

- In the presence of VI, LCI increases, i.e. the number of "turn-overs" needed to clear the inert marker gas, increases

Fuchs, Paeditr Respir Rev, 2011

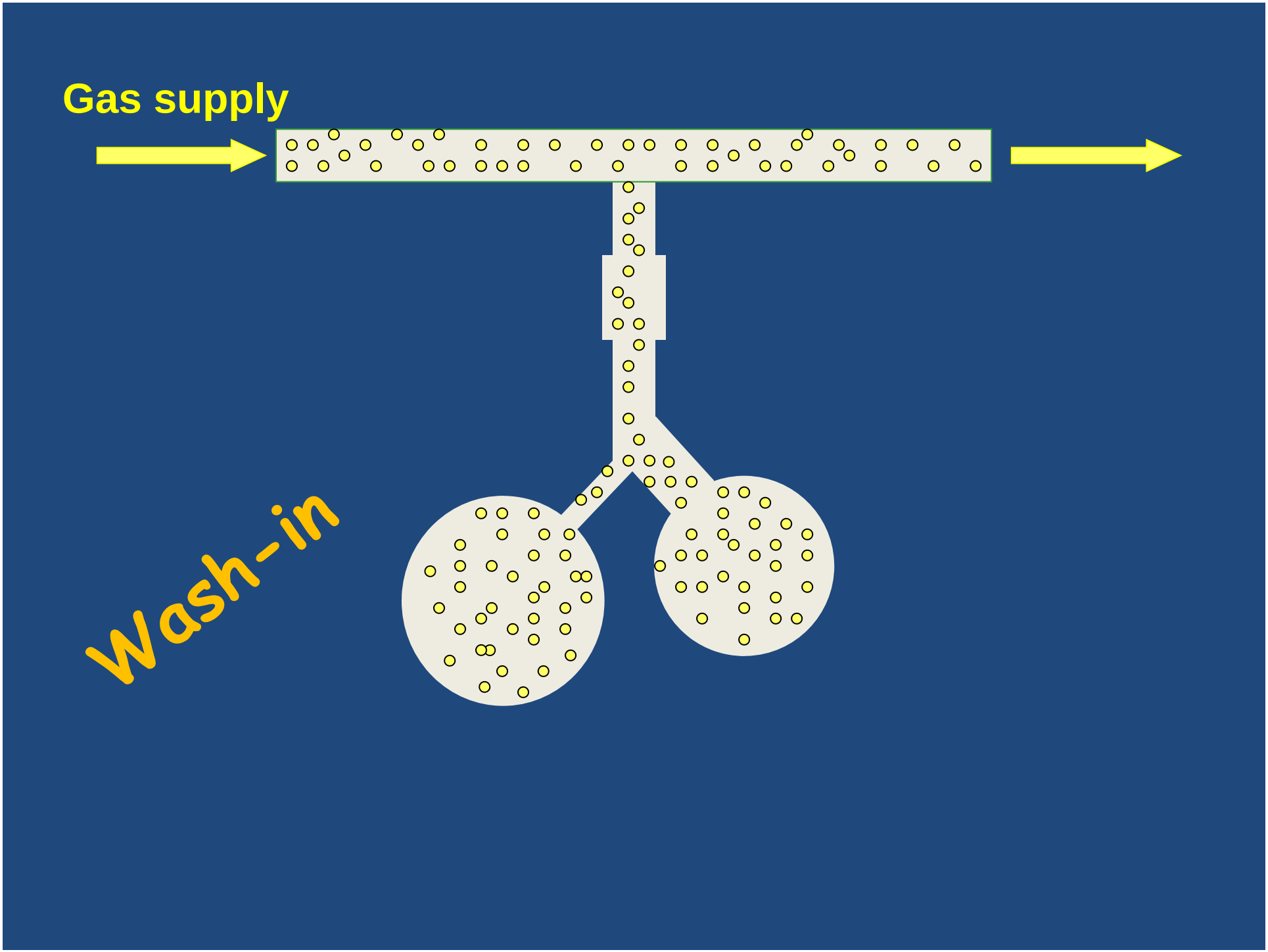
FRC

$$FRC = \frac{\text{Volume expired tracer gas (e.g. } SF_6)}{[SF_6]_{\text{startWO}} - [SF_6]_{\text{endWO}}}$$

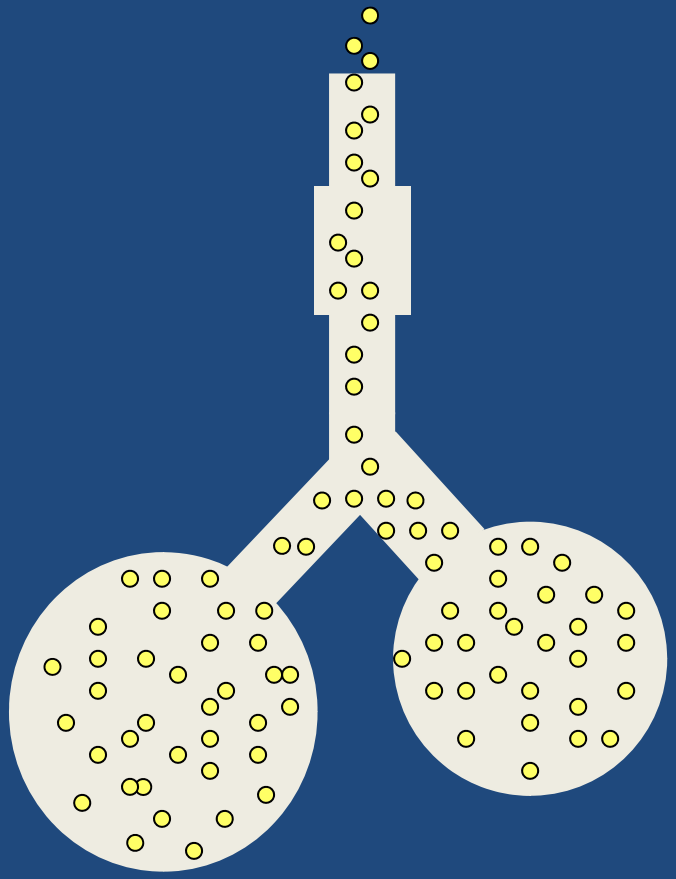
Equipment

- Mass spectrometer
- Ultrasonic technology
  - ✓ *Exhalyzer D*, Eco Medics AG
  - ✓ *EasyOne Pro*, MBW module, ndd medical
  - ✓ (*Innocor*)

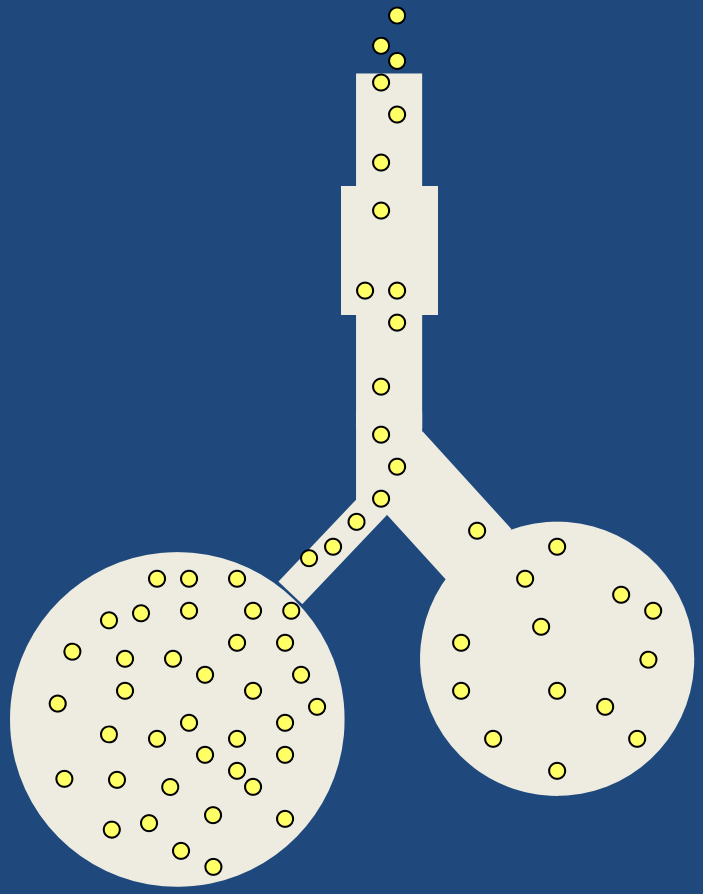
Fuchs, Paeditr Respir Rev, 2011


Gas supply
Wash-in

Wash-out

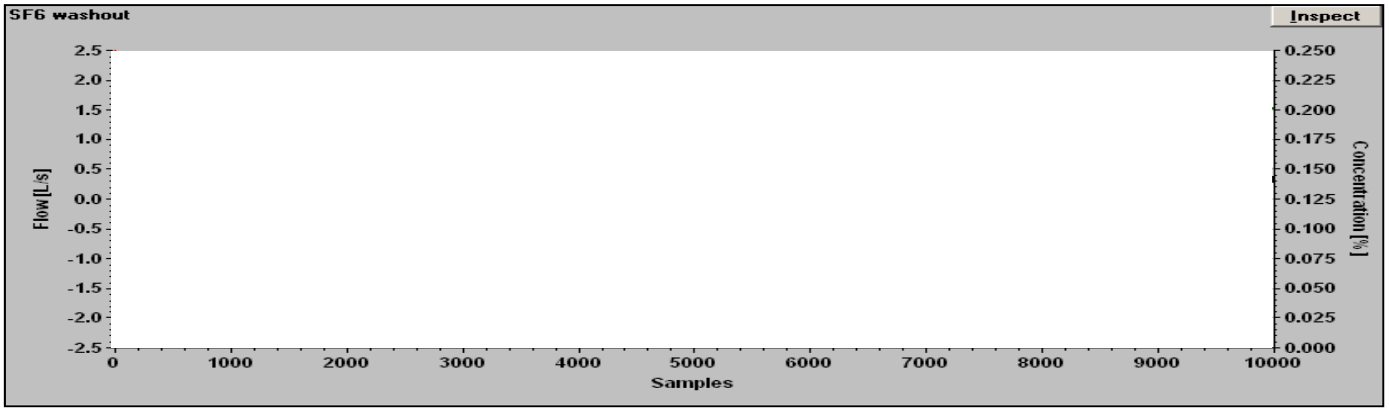


Ventilation inhomogeneity



Wash-out

Two balloons, sequential emptying

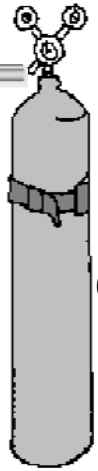


Flowpass circuit

Gas signal

Flowmeter

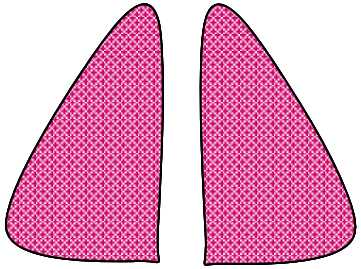
Flow signal



Gas Cylinder

SF_6

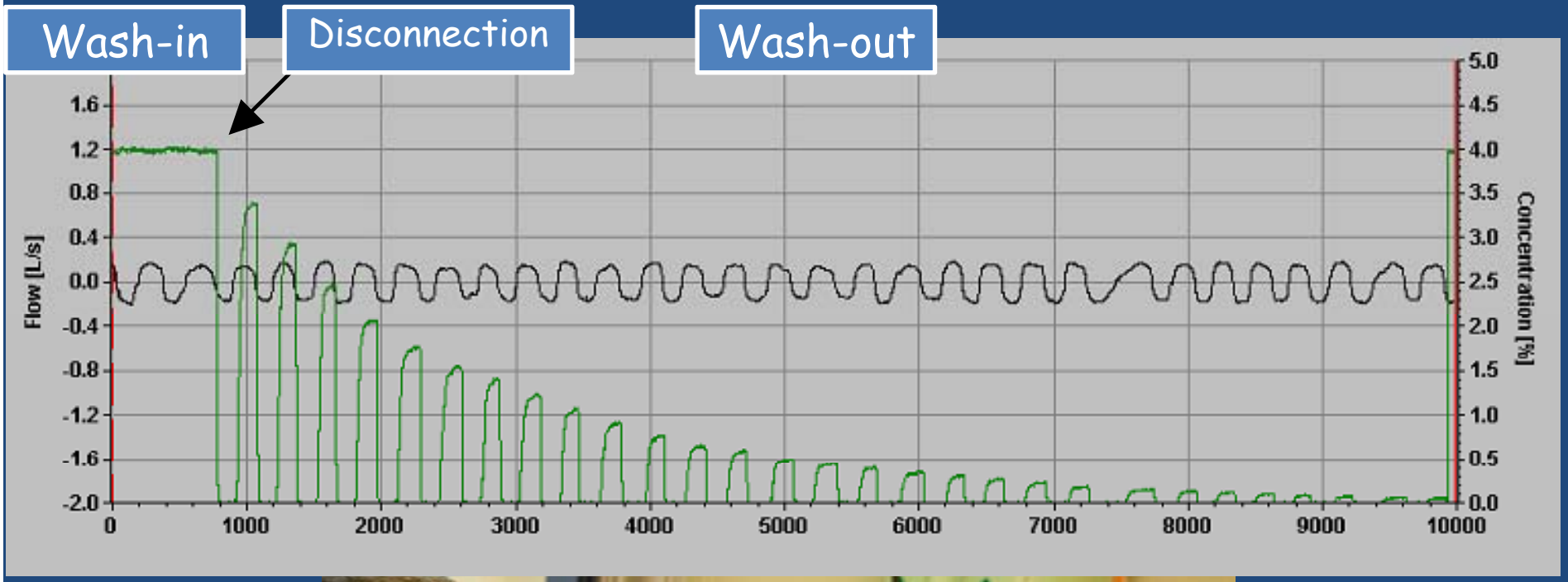
Wash-in

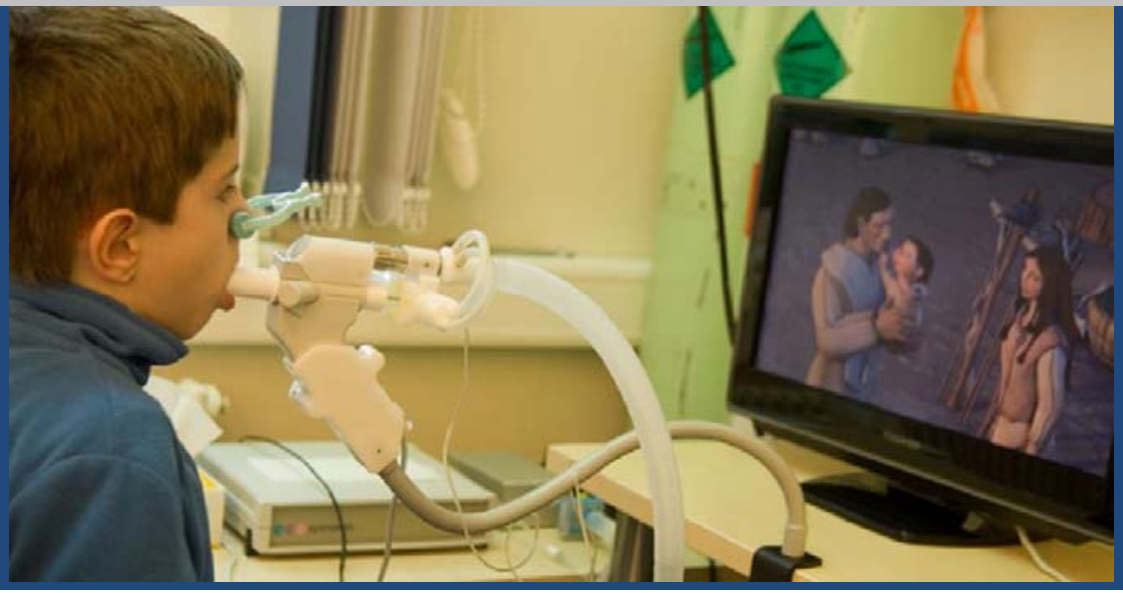


Wash-out

Patient lungs

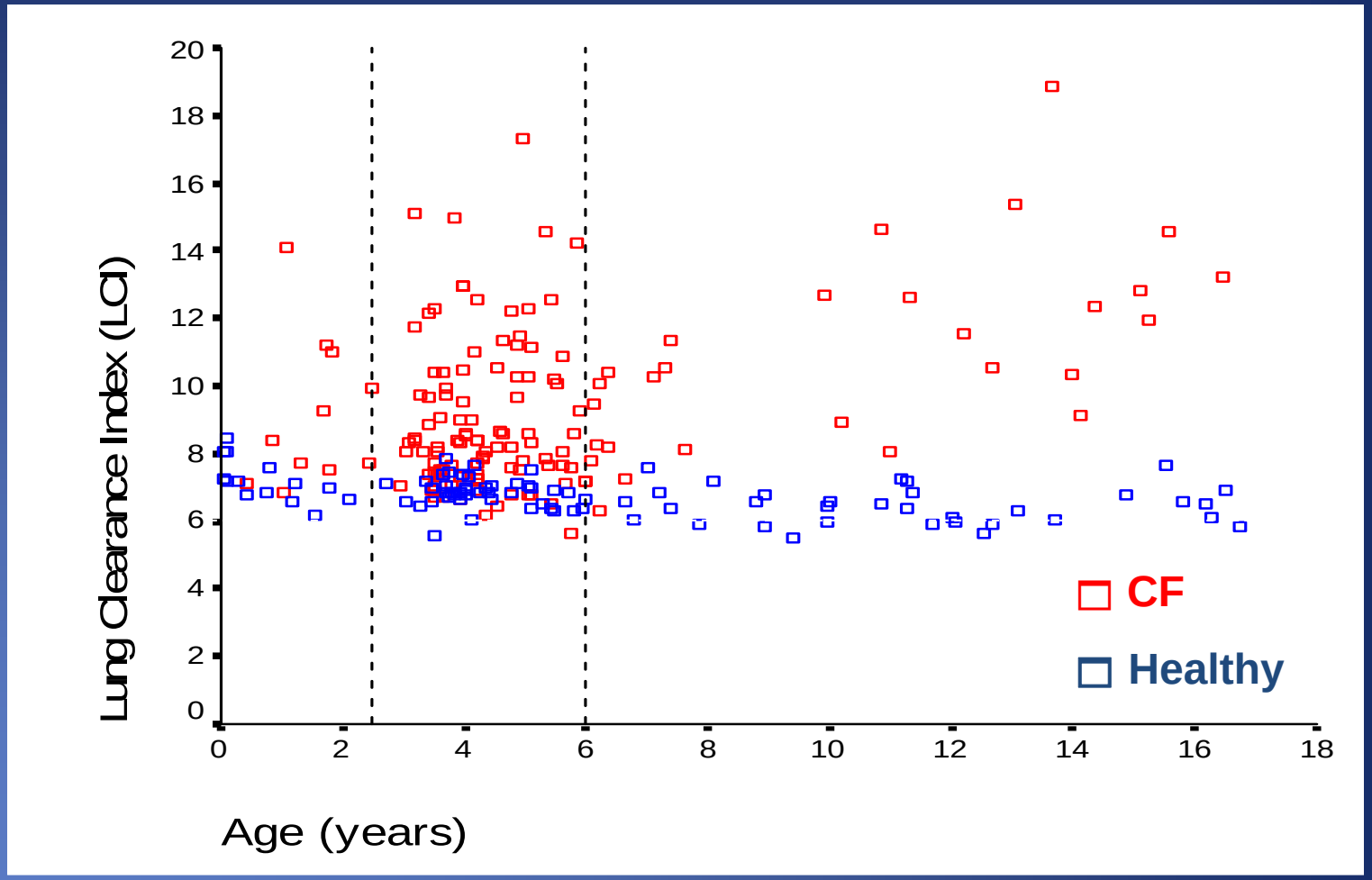
Adapted from Lung clearance index improves with treatment of an exacerbation in cystic fibrosis, by A. Horsley





Fuchs, Paeditr Respir Rev, 2011

Lung Clearance Index vs age in children with CF and healthy controls



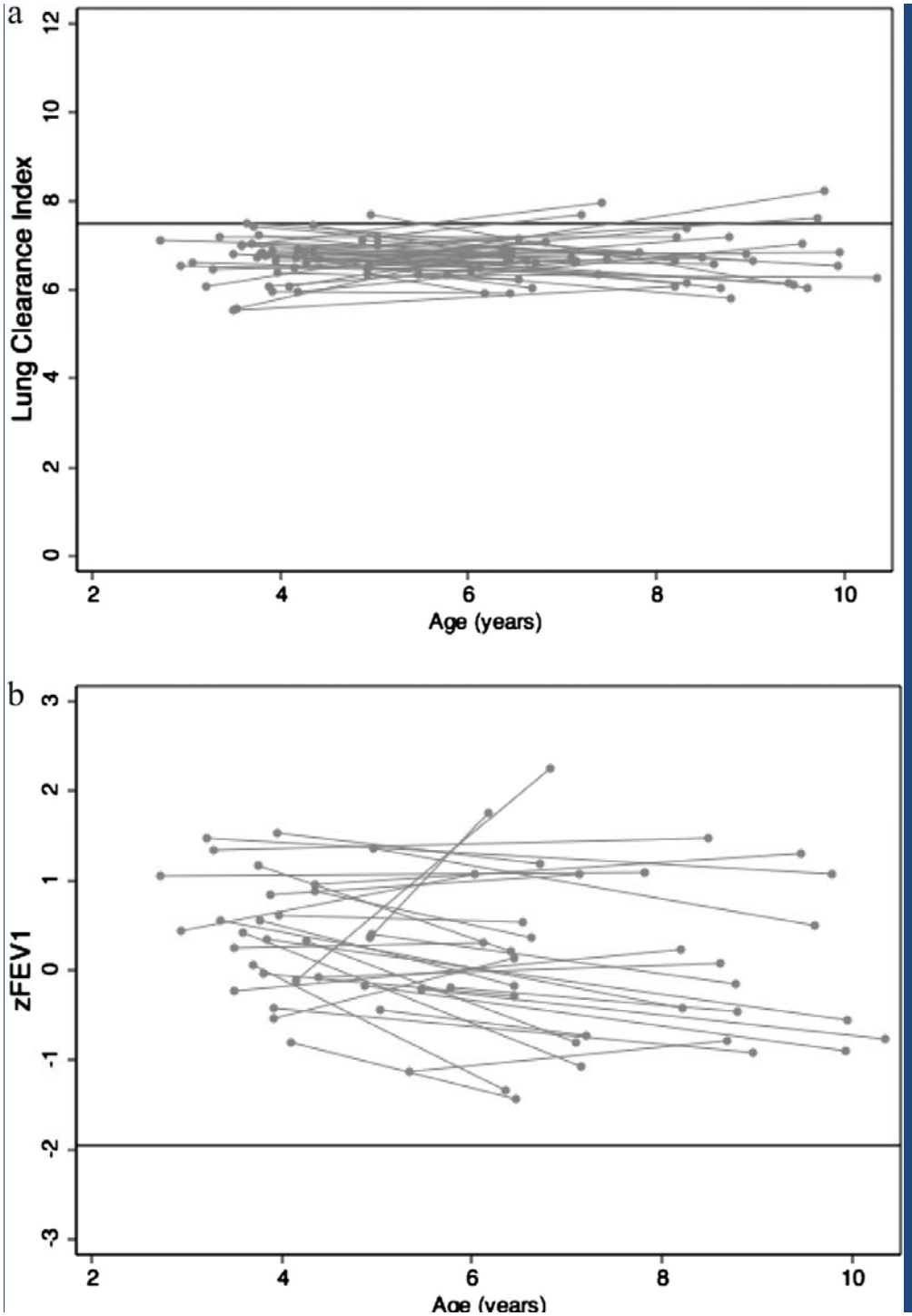
Aurora et al ; Thorax 2004, AJRCCM 2005, Resp Physiol Neuro 2005

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

Paul Aurora[1,2], Sanja Stanojevic[1,3], Angie Wade[3], Cara Oliver[2], Wanda Kozlowska[2], Sooky Lum[1], Andrew Bush[4], John Price[5], Siobhán B. Carr[6], Anu Shankar[7], and Janet Stocks[1]; on behalf of the London Cystic Fibrosis Collaboration*

- There is an urgent need for **alternative surrogates** that detect early lung disease and track through early childhood
- Spirometry and MBW
  - ✓preschool (3-5) and early school age (6-10)
  - ✓48 CF; 45 healthy children
- Preschool CF
  - ✓abnormal LCI in 35/48 (73%)
  - ✓abnormal FEV_1 in 10%
- Abnormal preschool LCI predicts subsequent lung function abnormalities

Am J Respir Crit Care Med Vol 183. pp 752–758, 2011

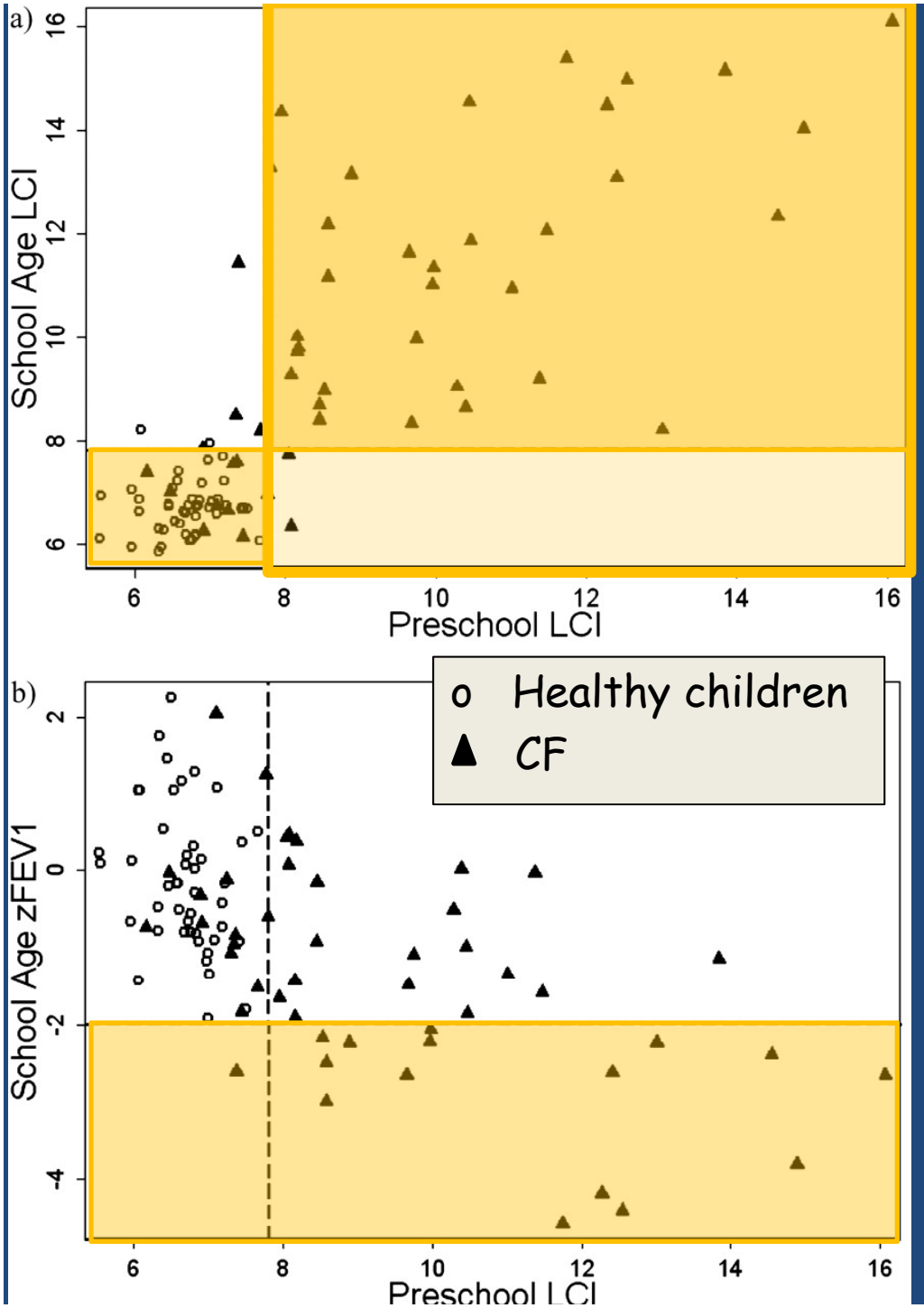


Longitudinal changes LCI and $zFEV_1$ for healthy children.

(A) LCI remains stable in health with an upper limit of normal of 7.8.

(B) Average change in $zFEV_1$ over time in healthy control subjects.

Aurora, Am J Respir Crit Care Med, 2011



Cross-plots of lung function results at preschool and early school age

- CF children with abnormal LCI at preschool age (n = 35, to the right of the vertical line) → abnormal at early school age in all but two children (*right lower quadrant).*
- Of the 13 children with normal preschool LCI, only 4 developed abnormal early school-age LCI (*upper left quadrant*).
- 15/35 (43%) of children with CF with abnormal LCI at preschool age had abnormal FEV_1 at early school age (*lower right quadrant*).
- Only 1 of those children with abnormal school-age FEV_1 had a normal preschool LCI (*lower left quadrant*).

Aurora, Am J Respir Crit Care Med, 2011

Assessment of pulmonary function by nitrogen washout and spirometry in preschool age children

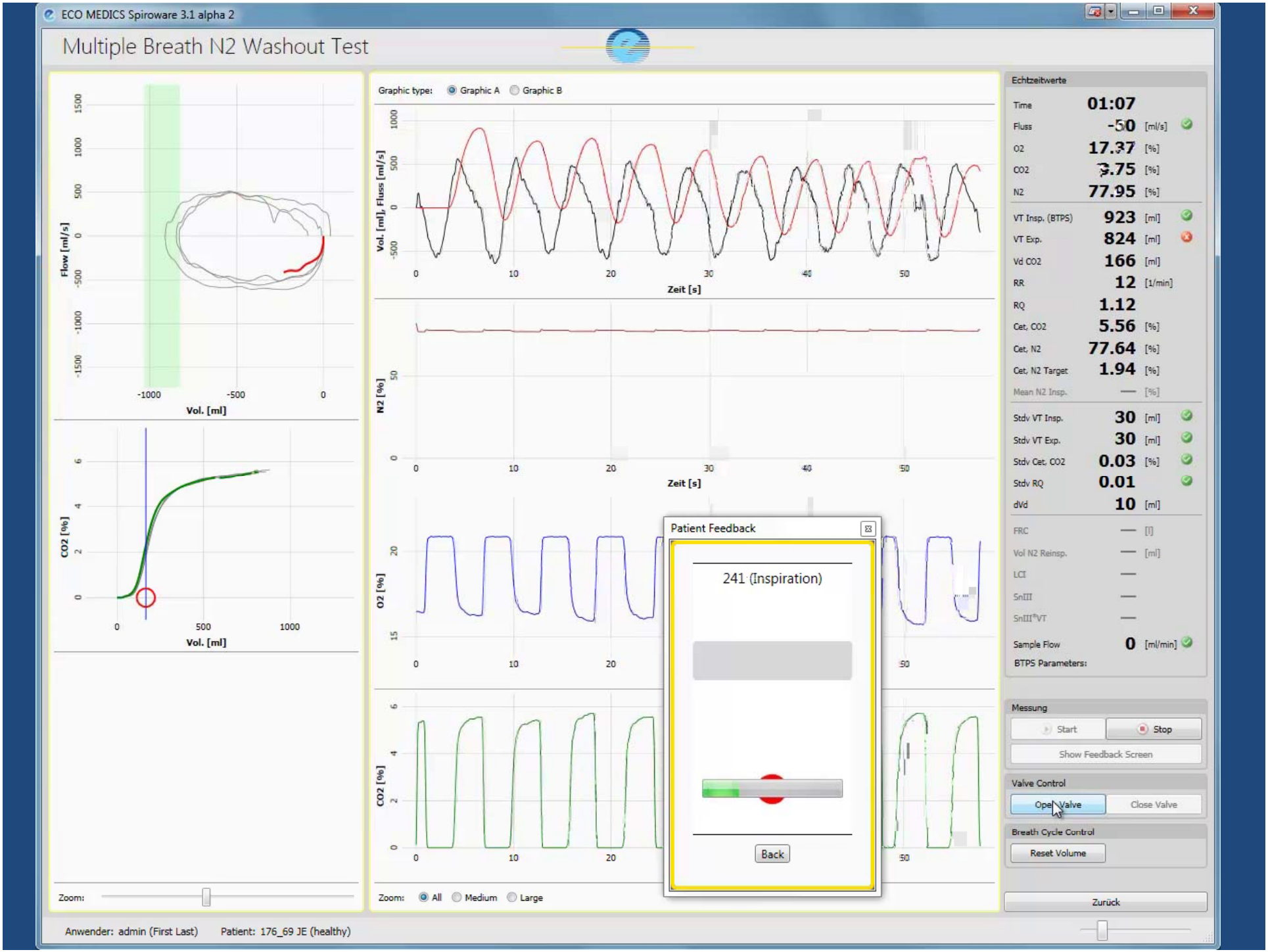
(pilot study)

Aims

- To evaluate the feasibility of performing MBW and spirometry in preschool children
- To detect differences in spirometry and ventilatory parameters between disease and control groups.

Methods

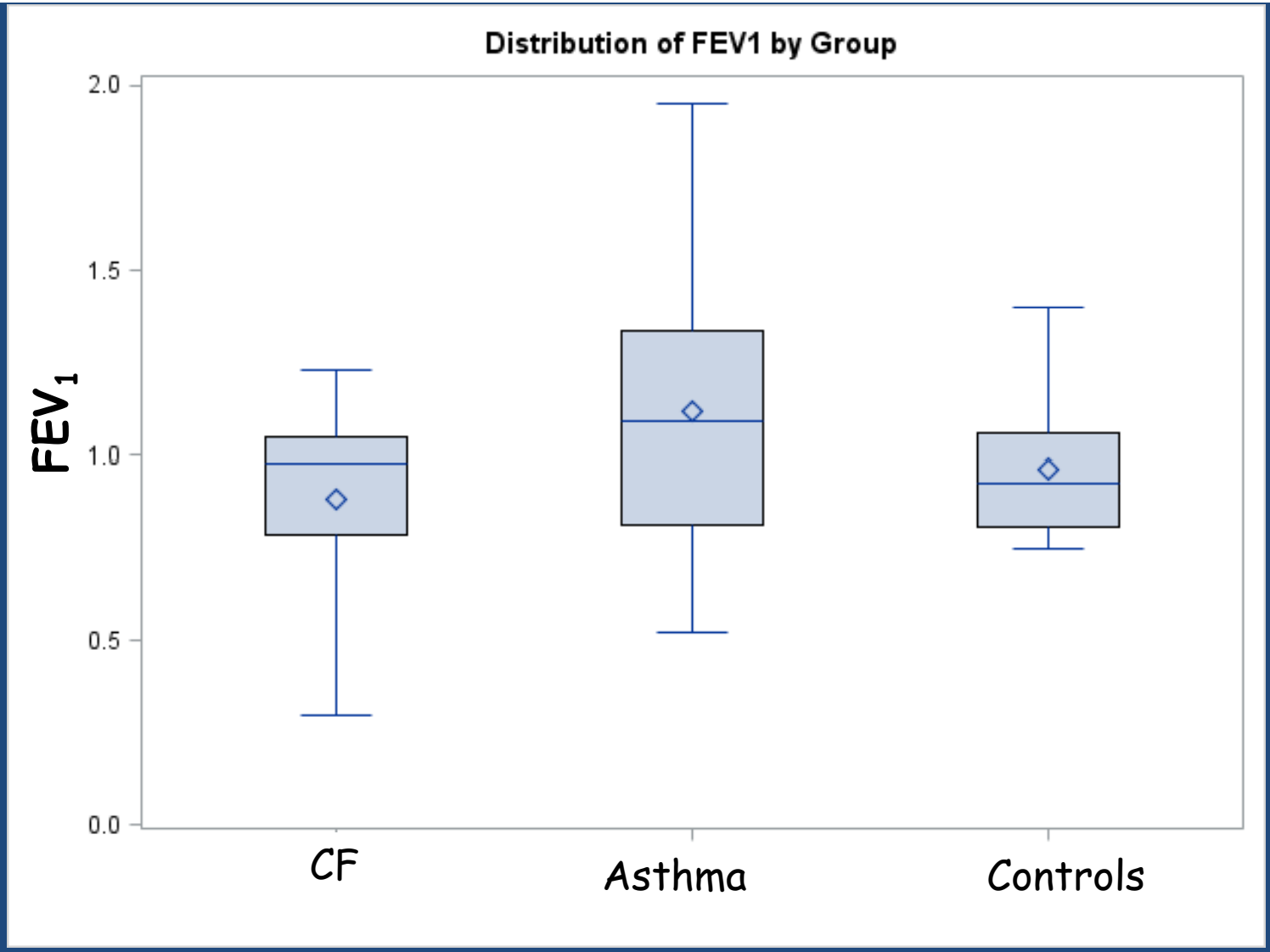
- Three groups of children aged 3-6 years
  - ✓ Children with confirmed diagnoses of CF
  - ✓ Children with a diagnosis of asthma (AS)
  - ✓ Children without a history of respiratory disease (HC).
- Multibreath Washout (MBW)
  - ✓ Tidal breathing
  - ✓ Nitrogen concentration analysis
  - ✓ Ultrasonic flow sensor (Exhalyzer, EcoMedics AG, Duerten, Switzerland).
- MBW was followed by spirometry and aiming to obtain at least 3 valid flow volume loops.


ECO MEDICS Spiroware 3.1 alpha 2
Multiple Breath N2 Washout Test
Flow [ml/s]
Vol. [ml]
CO2 [%]
Vol. [ml]
Zoom:
Graphic type: Graphic A Graphic B
Vol. [ml], Fluss [ml/s]
Zeit [s]
N2 [%]
Zeit [s]
O2 [%]
CO2 [%]
Zoom: All Medium Large
Patient Feedback
241 (Inspiration)
Back
Echtzeitwerte
Time 01:07
Fluss -50 [ml/s]
O2 17.37 [%]
CO2 3.75 [%]
N2 77.95 [%]
VT Insp. (BTPS) 923 [ml]
VT Exp. 824 [ml]
Vd CO2 166 [ml]
RR 12 [1/min]
RQ 1.12
Cet. CO2 5.56 [%]
Cet. N2 77.64 [%]
Cet. N2 Target 1.94 [%]
Mean N2 Insp. — [%]
Stdv VT Insp. 30 [ml]
Stdv VT Exp. 30 [ml]
Stdv Cet. CO2 0.03 [%]
Stdv RQ 0.01
dVd 10 [ml]
FRC — [l]
Vol N2 Reinsp. — [ml]
LCI —
SnIII —
SnIII*VT —
Sample Flow 0 [ml/min]
BTPS Parameters:
Messung
Start
Stop
Show Feedback Screen
Valve Control
Open Valve
Close Valve
Breath Cycle Control
Reset Volume
Zurück
Anwender: admin (First Last)
Patient: 176_69 JE (healthy)

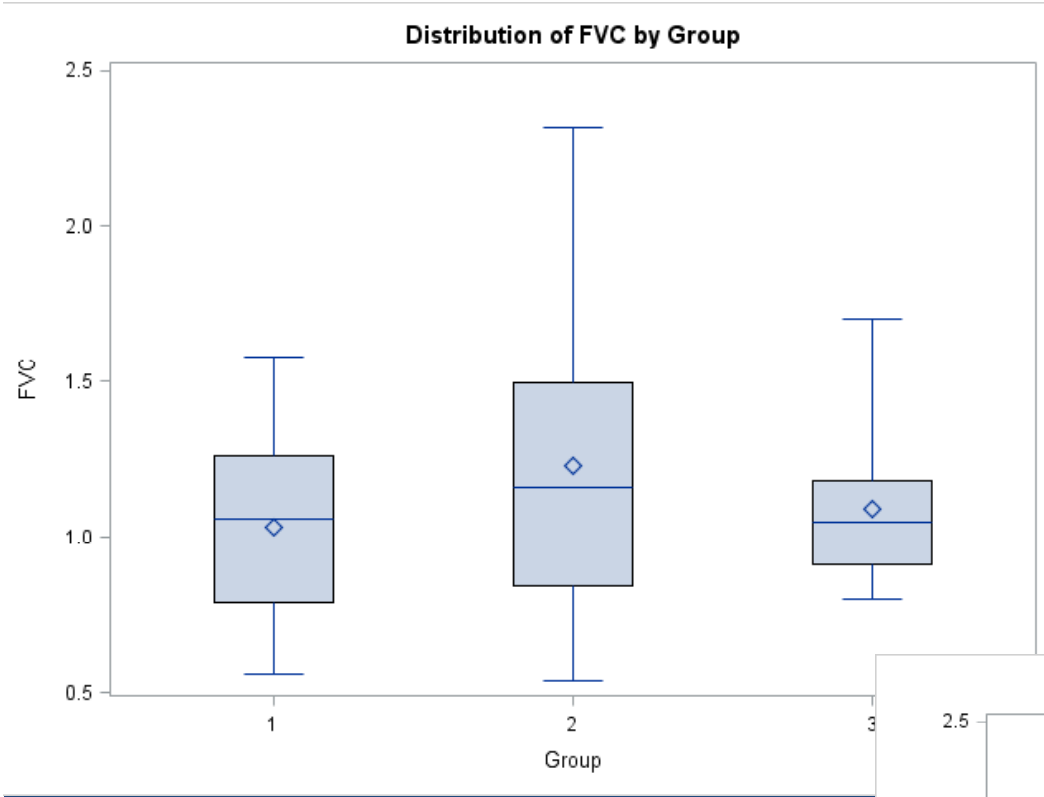
Results (pilot study)

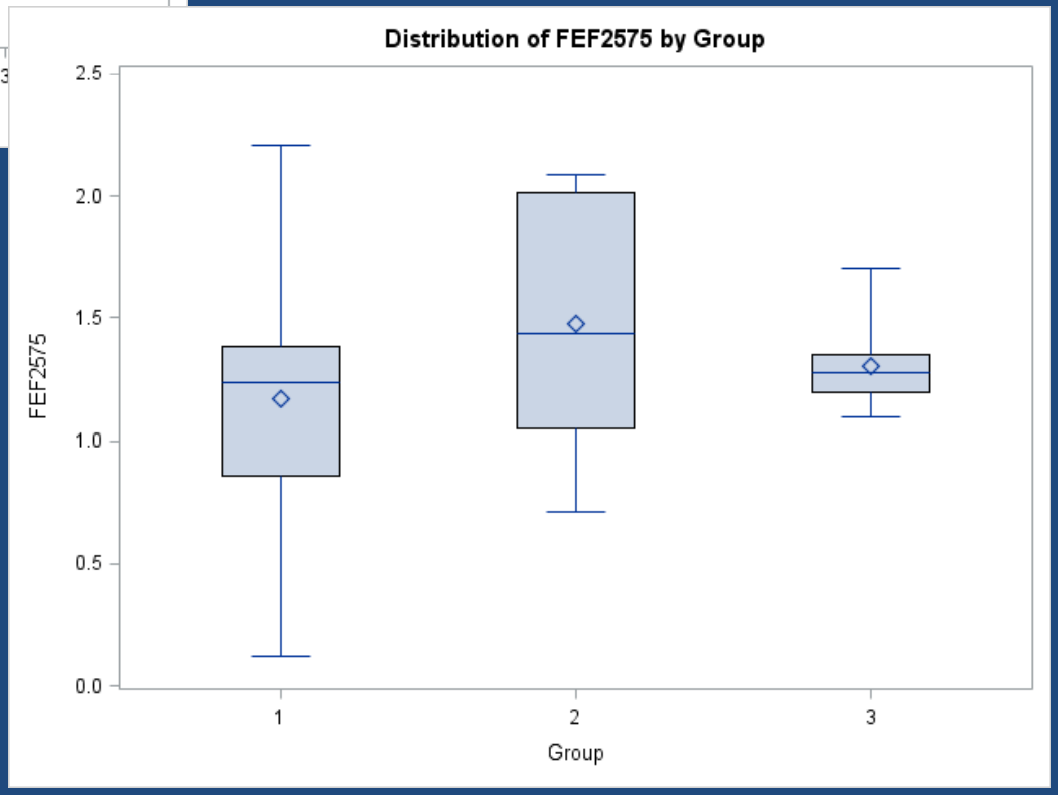
	CF	Asthma	Controls	p-value
n	23	15	12	
Age (years)	4.8 ± 1.1	4.3 ± 1.7	4.3 ± 0.8	0.3
Successful MBW	92%	85%	84%	0. 1
Successful spirometry	78%	73%	58%	0.03

- Children had less difficulty following the instructions for the MBW test than for spirometry (p=0.01)
- MBW: Break in the seal was the main reason for invalid tracings.
- Spirometry: Early termination was the main reason for invalid efforts.

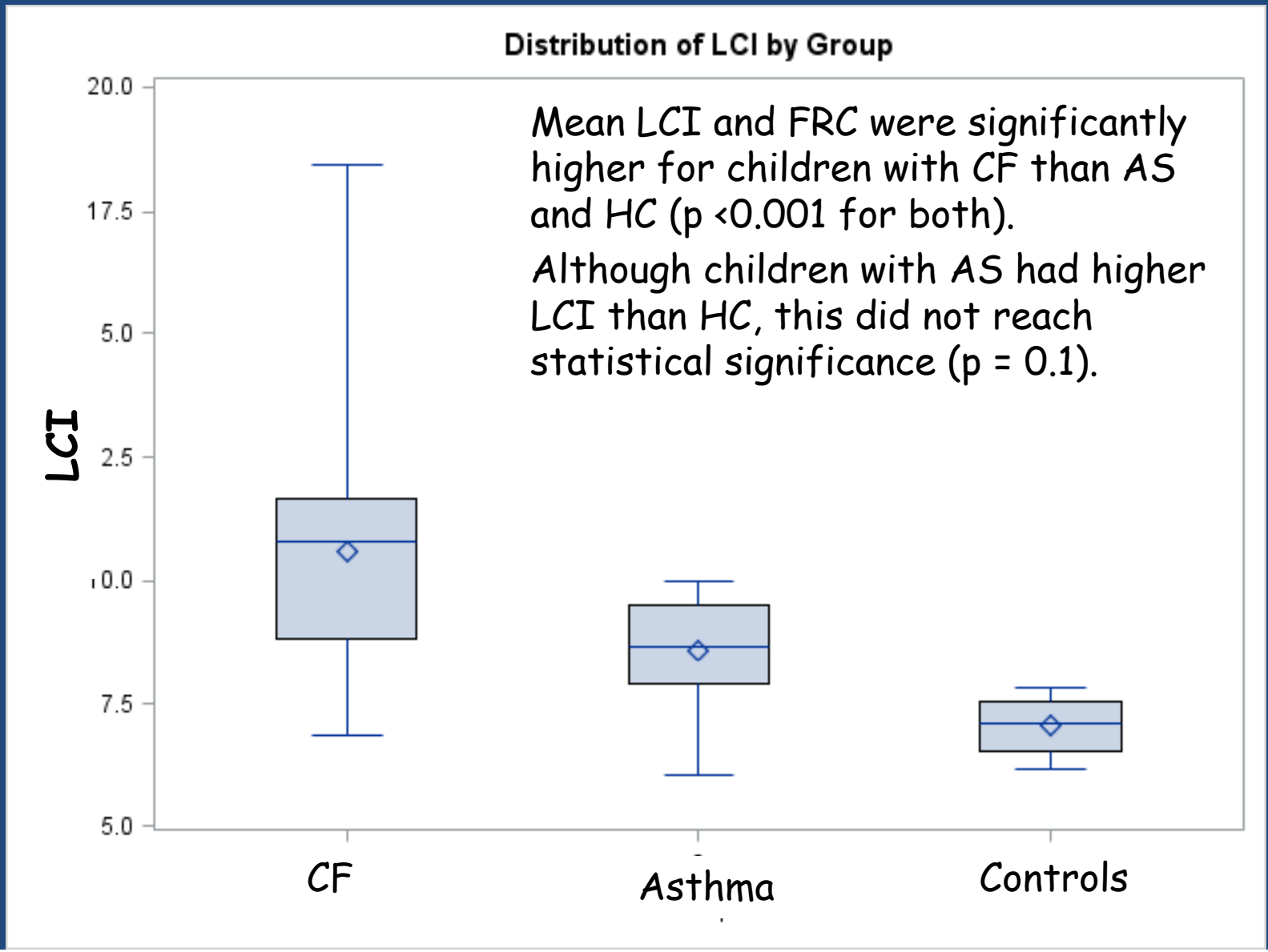


Distribution of spirometry parameters. Although for some children there was evidence for airway obstruction by spirometry (30% CF, 20% AS), no significant differences were noted between the study groups in FVC, FEV_1 and FEF_{25-75}.


Distribution of FVC by Group
FVC
2.5
2.0
1.5
1.0
0.5
1
2
3
Group


Distribution of FEF2575 by Group
FEF2575
2.5
2.0
1.5
1.0
0.5
0.0
1
2
3
Group

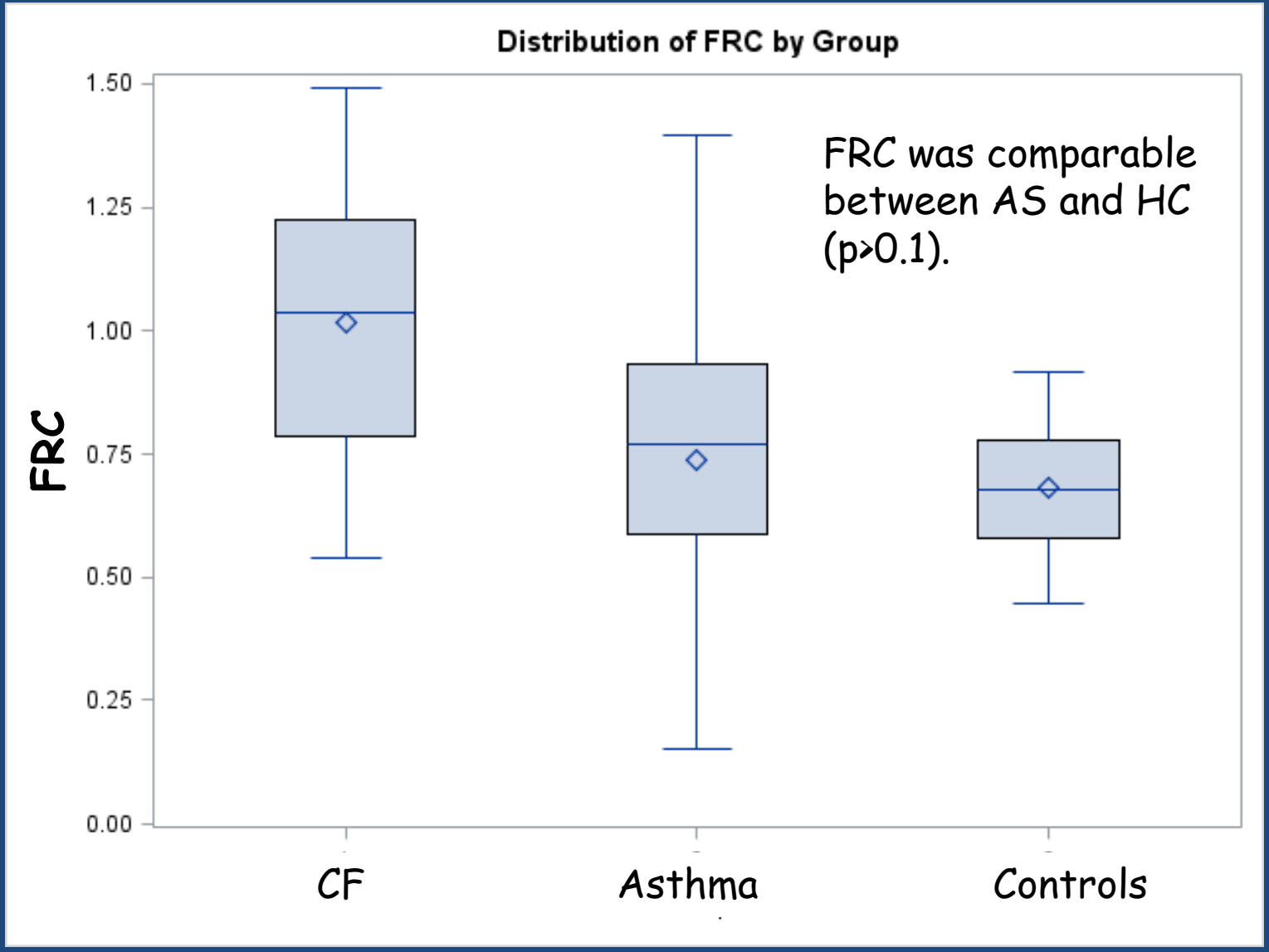
LCI by group


Distribution of LCI by Group
LCI
20.0
17.5
5.0
2.5
0.0
7.5
5.0
CF
Asthma
Controls
Mean LCI and FRC were significantly higher for children with CF than AS and HC (p <0.001 for both).
Although children with AS had higher LCI than HC, this did not reach statistical significance (p = 0.1).

Conclusions

- N_2 washout can be performed even in children unfamiliar with pulmonary function testing
- N_2 washout can detect defects in ventilatory function in preschool CF children distinguishing them from other populations

FRC by group


Distribution of FRC by Group
FRC
1.50
1.25
1.00
0.75
0.50
0.25
0.00
CF
Asthma
Controls
FRC was comparable between AS and HC (p>0.1).

ASSESSMENT OF PULMONARY FUNCTION BY NITROGEN WASHOUT AND SPIROMETRY IN PRESCHOOL AGE CHILDREN

Prais DM[1,2], Zirbes JM[1], Dunn CE[1], Everson C[1] and Milla CE[1].

[1] The Center for Excellence in Pulmonary Biology, Stanford University, Palo Alto, CA, USA

[2] Schneider's Children's Medical Center, Petach Tikvah, Israel

INTRODUCTION

- Pulmonary function assessment in children has the potential to identify the early manifestations of diseases like cystic fibrosis (CF).
- Children in the preschool age (3 – 6 years) have been identified as a challenging patient population for pulmonary function testing.
- Recent availability of Multibreath Washout (MBW) methodology based on indirect Nitrogen concentration analysis with a novel system that utilizes an ultrasonic flow sensor as well as O2 and CO2 sensors (Exhalyzer, EcoMedics AG, Duerten, Switzerland) has permitted wider applicability of MBW.
- We were interested in evaluating in children in the preschool age the performance characteristics of spirometry and ventilatory indices obtained from N2 washout as to their feasibility and ability to detect differences between disease and control groups.
- We hypothesized that MBW will be more sensitive to airway disease than spirometry.

METHODS

- Three groups of children between the ages of 3 and 6 years participated in this study:
  - Children with confirmed diagnoses of Cystic Fibrosis (CF) enrolled from the Stanford CF Center.
  - Children with a diagnosis of asthma (AS) enrolled from our asthma clinic as a disease control group.
  - Children without a history of respiratory disease and never exposed to cigarette smoke enrolled as healthy control group (HC).
- Children were studied during a period of stability (disease groups) and freedom from any acute symptomatology or illness.
- MBW by N2 washout was performed during tidal breathing and using 100% Oxygen. Three maneuvers free of artifact were obtained whenever possible and allowing for 2-times the washout time to lapse between maneuvers.
- The Functional residual capacity in Liters (FRC) and the Lung Clearance index (LCI) were estimated from the MBW.
- MBW was followed by spirometry and aiming to obtain at least 3 valid flow volume loops. Parameters were recorded as actual values in L or L/sec.
- All tests assessed for quality criteria following ATS/ERS recommendations.

RESULTS

- Children had less difficulty following the instructions for the MBW test than for spirometry.
- Good quality MBW tracings could be obtained in 92% of the children with CF, 85% of AS and 84% of HC ($p > 0.1$). Break in the seal was the main reason for invalid tracings.
- In contrast valid Spirometry could be obtained in 78% of CF, 73% AS, and 58% HC ($p = 0.03$). Early termination of effort was the main reason for invalid efforts.

Table 1. Characteristics of the children studied. Besides a larger representation of girls in the CF group, no other significant differences were noted.

	CF N = 23	Asthma N= 15	Healthy N = 12
Age	4.77 ± 1.1	4.32 ± 1.7	4.30 ± 0.8
Male:Female	4:19	8:7	6:6
Height	105.5 ± 13.1	103.6 ± 13.0	103.9 ± 7.5
Weight	18.1 ± 3.7	19.3 ± 5.9	17.85 ± 2.2
BMI	16.3 ± 2.3	17.5 ± 1.8	16.5 ± 1.1

Figure 1. Distribution of Spirometry parameters. Although for some children there was evidence for airway obstruction by Spirometry (30% CF, 20% AS), no significant differences were noted between the study groups in FVC, FEV1 and FEF_{25-75}.

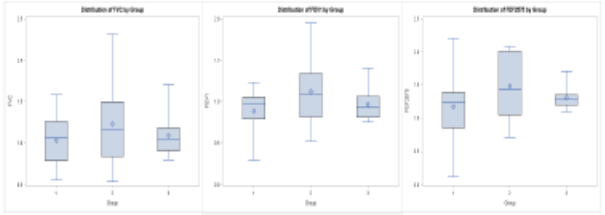
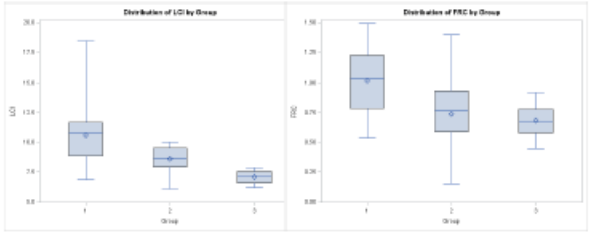


Figure 2. Distribution of MBW parameters. The mean LCI and FRC were significantly higher for children with CF than AS and HC ($p < 0.001$ for both comparisons). Although the children with AS had higher LCI than HC, this did not reach statistical significance ($p = 0.1$). FRC was comparable between AS and HC ($p > 0.1$).



CONCLUSIONS

- **N2 washout can be completed without difficulty even in children that have little familiarity with pulmonary function testing.**
- **Indices obtained from the N2 washout can detect defects in ventilatory function in children with CF that distinguishes them from other children.**