Assessment of Pediatric Lung Disease Using Multiple Breath Washout

Clement L. Ren, MD, MBA
Division of Pediatric Pulmonology, Allergy, and Sleep Medicine
Riley Hospital for Children and Indiana University School of Medicine
Indianapolis, IN USA
Gas Transport in the Lung

Diffusion across alveolar-capillary membrane

Multiple Breath Washout (MBW)

Tracer Gas Options:
• $\text{SF}_6$
• Helium

N₂ MBW Technique

Wash-out Phase

100% Oxygen

Time [s]

80%

2.5%

M₂ [%]
Increased Washout Time Due to Impaired Ventilation

RC Darling, JCI 1940
Lung Clearance Index (LCI)

- LCI is the # of lung turnovers required to clear the lungs of tracer gas or N₂ 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 \( \Rightarrow \) More ventilation inhomogeneity

LCl: Normal vs Abnormal

Normal

Abnormal
Multiple Breath Washout and the Lung Clearance Index

<table>
<thead>
<tr>
<th>Subj.</th>
<th>Diagnosis</th>
<th>Sex</th>
<th>Age (yrs.)</th>
<th>Tidal vol. (ml.)</th>
<th>Resp. (per min.)</th>
<th>Ventilatory components</th>
<th>Average interval N₂ molecules remained</th>
<th>Pul. N₂ clearance delay (%)</th>
<th>FRC (ml.)</th>
<th>Σ VL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>f₁  w₁  f₂  w₂  f₃  w₃</td>
<td>No. breaths</td>
<td>Ideal</td>
<td>Actual</td>
<td>Ideal</td>
</tr>
<tr>
<td>E. R.</td>
<td>Asthma</td>
<td>F</td>
<td>34</td>
<td>710</td>
<td>17</td>
<td>.46  .911  .54  .694</td>
<td>6.87  4.51  .41  .27</td>
<td>52</td>
<td>2,530</td>
<td>1,910</td>
</tr>
<tr>
<td>V. J.</td>
<td>mild</td>
<td>F</td>
<td>33</td>
<td>364</td>
<td>25</td>
<td>.71  .936  .29  .870</td>
<td>13.3  11.6  .53  .47</td>
<td>13</td>
<td>2,000</td>
<td>2,310</td>
</tr>
<tr>
<td>L. S.</td>
<td>moderate</td>
<td>M</td>
<td>16</td>
<td>352</td>
<td>22</td>
<td>.54  .979  .38  .950  .08  .722</td>
<td>33.5  17.2  1.5  .78  95</td>
<td>3,970</td>
<td>4,720</td>
<td></td>
</tr>
<tr>
<td>J. K.</td>
<td>severe</td>
<td>M</td>
<td>41</td>
<td>482</td>
<td>20</td>
<td>.53  .987  .47  .882</td>
<td>44.5  15.4  2.2  .77  190</td>
<td>3,250</td>
<td>3,750</td>
<td></td>
</tr>
<tr>
<td>G. D.</td>
<td>Emphysema</td>
<td>M</td>
<td>70</td>
<td>437</td>
<td>17</td>
<td>.79  .980  .21  .844</td>
<td>40.7  18.9  2.4  1.1  115</td>
<td>4,600</td>
<td>4,370</td>
<td></td>
</tr>
<tr>
<td>N. R.</td>
<td>severe</td>
<td>M</td>
<td>58</td>
<td>312</td>
<td>22</td>
<td>.87  .990  .13  .820</td>
<td>87.5  27.8  4.0  1.3  215</td>
<td>4,680</td>
<td>3,710</td>
<td></td>
</tr>
<tr>
<td>J. C.</td>
<td>severe</td>
<td>M</td>
<td>59</td>
<td>395</td>
<td>20</td>
<td>.72  .991  .25  .926  .03  .622</td>
<td>83.4  24.4  4.2  1.2  240</td>
<td>4,670</td>
<td>4,600</td>
<td></td>
</tr>
<tr>
<td>W. A.</td>
<td>severe—asthma</td>
<td>M</td>
<td>60</td>
<td>497</td>
<td>16</td>
<td>.72  .981  .20  .862  .08  .603</td>
<td>39.7  11.4  2.6  0.74  248</td>
<td>3,880</td>
<td>3,440</td>
<td></td>
</tr>
<tr>
<td>S. F.</td>
<td>severe—asthma</td>
<td>M</td>
<td>66</td>
<td>467</td>
<td>19</td>
<td>.82  .981  .16  .858  .02  .418</td>
<td>44.5  16.7  2.3  0.88  166</td>
<td>4,250</td>
<td>4,180</td>
<td></td>
</tr>
<tr>
<td>J. P.</td>
<td>Congestive heart failure minimal</td>
<td>M</td>
<td>40</td>
<td>307</td>
<td>26</td>
<td>.86  .934  .14  .779</td>
<td>13.7  10.9  .53  .42  25</td>
<td>2,070</td>
<td>1,730</td>
<td></td>
</tr>
<tr>
<td>J. B.</td>
<td>moderate</td>
<td>M</td>
<td>39</td>
<td>574</td>
<td>13</td>
<td>.48  .953  .52  .771</td>
<td>12.5  6.07  .96  .52  89</td>
<td>2,400</td>
<td>2,170</td>
<td></td>
</tr>
<tr>
<td>G. B.</td>
<td>severe</td>
<td>F</td>
<td>39</td>
<td>451</td>
<td>30</td>
<td>.61  .847  .39  .626</td>
<td>5.0  3.09  .17  .13  29</td>
<td>1,580</td>
<td>1,030</td>
<td></td>
</tr>
<tr>
<td>E. W.</td>
<td>severe</td>
<td>F</td>
<td>36</td>
<td>320</td>
<td>32</td>
<td>.45  .972  .48  .926  .07  .752</td>
<td>23.4  14.7  .73  .46  60</td>
<td>2,330</td>
<td>2,700</td>
<td></td>
</tr>
<tr>
<td>G. W.</td>
<td>severe—with (?) silicosis</td>
<td>M</td>
<td>56</td>
<td>492</td>
<td>27</td>
<td>.78  .876  .22  .841</td>
<td>33.7  16.7  1.25  .62  102</td>
<td>4,570</td>
<td>5,560</td>
<td></td>
</tr>
<tr>
<td>B. T.</td>
<td>Bronchiectasis, L. lower lobectomy, 8 mos. pregnant</td>
<td>F</td>
<td>22</td>
<td>670</td>
<td>14</td>
<td>.17  .966  .75  .810  .08  .304</td>
<td>9.05  3.73  .65  .27  143</td>
<td>1,660</td>
<td>1,590</td>
<td></td>
</tr>
<tr>
<td>E. T.</td>
<td>Sarcoid-pulmonary cyst</td>
<td>F</td>
<td>26</td>
<td>400</td>
<td>31</td>
<td>.69  .973  .31  .850</td>
<td>27.6  14.3  .90  .46  93</td>
<td>3,330</td>
<td>2,640</td>
<td></td>
</tr>
<tr>
<td>T. C.</td>
<td>Pulmonary fibrosis</td>
<td>M</td>
<td>34</td>
<td>392</td>
<td>21</td>
<td>.48  .980  .47  .938  .05  .393</td>
<td>31.6  9.31  1.51  .45  233</td>
<td>2,020</td>
<td>2,760</td>
<td></td>
</tr>
<tr>
<td>L. W.</td>
<td>3 mos. post-pneumonec-tomy</td>
<td>M</td>
<td>65</td>
<td>430</td>
<td>23</td>
<td>.48  .961  .37  .892  .15  .635</td>
<td>16.1  7.75  .70  .34  108</td>
<td>1,850</td>
<td>1,750</td>
<td></td>
</tr>
<tr>
<td>A. G.</td>
<td>2 wks. post-pneumo-nec-tomy</td>
<td>M</td>
<td>54</td>
<td>556</td>
<td>24</td>
<td>.55  .952  .37  .885  .08  .498</td>
<td>14.5  7.40  .61  .31  97</td>
<td>2,700</td>
<td>2,040</td>
<td></td>
</tr>
</tbody>
</table>
Other MBW Measurements

• \( \text{LCI}_{5.0} \) = Number of lung turnovers required to reach 1/20 (5%) of original concentration
  o Faster to measure than \( \text{LCI}_{2.5} \)
  o Easier for young children to perform
  o Less sensitive than \( \text{LCI}_{2.5} \)

• Normalized slope of phase III
  o \( S_{\text{cond}} \): Convection dependent inhomogeneity
  o \( S_{\text{acin}} \): 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

$S_{\text{cond}}$ and $S_{\text{acin}}$

Gas transport within the lung

$S_{\text{cond}}$: Convection dependent inhomogeneity

$S_{\text{acin}}$: 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
• ↑ M1/M0 or M2/M0 → ↑ Ventilation Inhomogeneity
• Moment ratios
  o Potentially more sensitive than LCI
  o More difficult to calculate
  o Role in clinical care and research requires further study

# Tracer Gas Selection

<table>
<thead>
<tr>
<th>Tracer Gas</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Sulfur Hexafluoride (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

<table>
<thead>
<tr>
<th>Device</th>
<th>Tracer gas</th>
<th>FDA Approved?</th>
<th>Comments</th>
</tr>
</thead>
</table>
| 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
CO₂ sensor
Connection to gas source
Sampling port for O₂ measurement

Flow, CO₂, and O₂ are measured at different points in the circuit:
Signals must be synchronized

N₂ concentration = 100% - (CO₂ conc + O₂ 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

<table>
<thead>
<tr>
<th></th>
<th>Mouthpiece and Nose-Clip</th>
<th>Facemask</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distractions</td>
<td>Oral stimulation (e.g. chewing)</td>
<td>Avoids oral stimulation</td>
</tr>
<tr>
<td>Equipment Dead Space</td>
<td>Defined</td>
<td>Difficult to Define</td>
</tr>
<tr>
<td>Seal and Risk of Leak</td>
<td>Determined by subject</td>
<td>Operator determined</td>
</tr>
<tr>
<td>Impact of Nasal Airways</td>
<td>Removed</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
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
- $\geq$3 breaths with concentration $\leq1/40$ of initial concentration
- 3 reproducible maneuvers (values within 10% of each other)

MBW Quality Control: Training is Key!

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

Flow

Volume

Stable End Expiratory Level; no sudden shifts
Unacceptable MBW: Shifting EEL

Shifting EEL = Shifting FRC

EEL sudden shifts
Unacceptable MBW: Leak
Acceptable MBW: Unsynchronized Signals

Signals can be manually synchronized after the test.
Challenges and Limitations of Infant MBW

• Tracer gas challenges
  o SF6: Needs mass spectrometer
  o N2 washout: O2 affects breathing pattern
    ▪ Can potentially overcome this by prebreathing at 30% FiO2

• 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
65% of children with normal FEV1 had an abnormal LCI

PM Gustafsson, et al Thorax 2008
Preschool LCI Predicts School Age FEV1

![Graph showing relation between preschool LCI and school age zFEV1]

P Aurora, et al. AJRCCM 2011
LCI in Preschoolers with CF

S Stanojevic, et al. AJRCCM 2017
Hypertonic Saline and DNase Lower LCI in CF


Riley Hospital for Children
Indiana University Health

SCHOOL OF MEDICINE
INDIANA UNIVERSITY

Dornase alfa
placebo
DNase

Hypertonic saline

LCl

weeks

MBW in CF: Other Studies

• LCI improves in response to other CF therapies
  o Ivacaftor
  o Hypertonic saline in infants and preschoolers

• LCI correlates with
  o Bronchiectasis seen on chest CT
  o Infection and inflammation

• Variable changes in LCI after treatment of pulmonary exacerbation
  o Potential for treatment to open up poorly ventilated units
## LCI in Asthma

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Asthma</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD) FEV\textsubscript{1} z-score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>−2.64–1.28</td>
<td>−4.00–1.82</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Mean (SD) LCI (CEV/FRC)</strong></td>
<td>6.24 (0.47)</td>
<td>6.69 (0.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>Range</td>
<td>5.14–7.05</td>
<td>5.49–9.46</td>
<td></td>
</tr>
<tr>
<td><strong>Mean (SD) S\textsubscript{cond}, Vt corrected</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>−0.03–0.06</td>
<td>−0.01–0.09</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Mean (SD) S\textsubscript{achin}, Vt corrected</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.02–0.29</td>
<td>0.05–0.40</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Mean (SD) Vt (l)</strong></td>
<td>0.55 (0.24)</td>
<td>0.45 (0.17)</td>
<td>0.07</td>
</tr>
<tr>
<td>Range</td>
<td>0.19–0.99</td>
<td>0.23–0.80</td>
<td></td>
</tr>
<tr>
<td><strong>Mean (SD) FRC (l)</strong></td>
<td>2.14 (1.02)</td>
<td>1.91 (0.78)</td>
<td>0.31</td>
</tr>
<tr>
<td>Range</td>
<td>0.80–4.51</td>
<td>0.85–3.82</td>
<td></td>
</tr>
</tbody>
</table>
MBW in Asthma vs CF

## LCI in PCD

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

47% of patients with normal FEV1 had an abnormal LCI.

M Boon et al; Thorax 2015
LCI in PCD and CF

- 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.

* Represents ratio of geometric means, using exponentiated parameter estimates from log-transformed data
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
LCI in Extremely Preterm Children

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

S Lum, ERJ 2011
# LCI in Pediatric Lung Diseases

<table>
<thead>
<tr>
<th></th>
<th>Relative increase in LCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>PCD</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Asthma</td>
<td>↑</td>
</tr>
<tr>
<td>BPD</td>
<td>↑</td>
</tr>
</tbody>
</table>
Application of MBW to Research and Clinical Care

• Research
  o Most useful for CF and PCD
  o Study populations
    ▪ Young children
    ▪ Mild disease
  o Infant MBW is very challenging

• Limitations/challenges for clinical use
  o Time
  o Billing
  o Technical expertise
  o 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