The lung clearance index in young infants: impact of tidal volume and dead space

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The lung clearance index in young infants: impact of tidal volume and dead space

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Abstract

Lung clearance index (LCI), measured by multiple breath washout (MBW), is one of the most frequently used measures of ventilation inhomogeneity. This study was designed to investigate the effect of lung volumes on LCI in young infants. The dependence of LCI on dead space volume ($V_D$), tidal volume ($V_T$) and functional residual capacity (FRC) was investigated by mathematical modeling and by MBW measurements using sulfur hexafluoride ($SF_6$) as a tracer gas. MBW was performed in 150 infants, of median postmenstrual age 46.7 weeks, followed up after neonatal intensive care. Wheezing was assessed in 90 of these infants by computerized respiratory sound analysis during quiet sleep. The strongest correlation was observed between LCI and the volume ratios $V_T$/FRC (Spearman rank order correlation coefficient $Rs = 0.688$, $p < 0.001$), $V_D$/FRC ($Rs = 0.733$, $p < 0.001$) and $V_D$/V_T ($Rs = 0.854$, $p < 0.001$). LCI calculated from $V_D$, $V_T$, and FRC was linearly related to measured LCI with a coefficient of determination of 75%. There were no significant differences between wheezers and non-wheezers in postmenstrual age and body weight, but FRC was significantly increased ($p < 0.001$) and median (interquartile range) LCI significantly decreased (5.83 (5.45–6.51) versus (6.54 (6.03–7.22), $p < 0.001$) in wheezing compared to non-wheezing infants. Model calculations also showed that LCI was significantly reduced in wheezing infants (5.09 (4.79–5.62) versus 5.43 (5.08–5.82), $p < 0.018$), indicating that the reduction can be explained by differences in the lung volumes, not by improved ventilation homogeneity. In conclusion, the strong dependence of LCI on lung volumes in young infants can lead to misinterpretations regarding the homogeneity of alveolar ventilation.
Keywords: multiple-breath washout techniques, lung clearance index, modeling, lung injury, infants

Online supplementary data available from stacks.iop.org/PM/36/071601/mmedia

(Some figures may appear in colour only in the online journal)

Abbreviations

- $V_d$: dead space volume
- $V_T$: tidal volume
- FRC: functional residual capacity
- LCI: lung clearance index
- LCI$_{predicted}$: LCI calculated from lung volumes
- $R^2$: coefficient of determination
- $R_s$: Spearman rank order correlation coefficient
- MBW: multiple breath washout
- MANOVA: multivariate analysis of variance

Introduction

Several lung diseases in newborns and young infants are characterized by unevenness of alveolar ventilation due to impaired lung development, inflammation, airway narrowing and/ or airway wall structural damage (Aurora et al 2005b). Surfactant deficiency or dysfunction may increase this inhomogeneity by collapse or over-distention of the alveoli (Sandberg et al 1997). Ventilation inhomogeneity affects overall gas exchange in the lungs, and several indices have been developed (e.g. lung clearance index (LCI), moment ratios, alveolar mean dilution numbers) to quantify the degree of inhomogeneity of alveolar ventilation (Saidel et al 1975, Habib and Lutchen 1991, Pillow et al 2006).

LCI derived from a multiple breath tracer gas washin or washout (MBW) curve is the most frequently reported measure of ventilation inhomogeneity in infants because it is clearly defined and easy to comprehend. The LCI describes the number of turnovers of end-expiratory lung volume required to reduce end tidal tracer gas concentration to one-fortieth of the starting concentration. Inhomogeneities in alveolar ventilation will result in an increase in the number of turnovers required to reduce the concentration of tracer gas. The measurement does not require active cooperation and can be performed in ventilated and sedated infants (Proquitte et al 2010, Landolfo et al 2013). The concept of this index was first developed at the begin of the fifties (Becklake 1952) and the use of one-fortieth as a cut-off value is due to the linear operating ranges of early nitrogen analyzers (Horsley 2009).

The availability of commercial equipment and the recently published ERS/ATS consensus statement (Robinson et al 2013) on inert gas washout tests have renewed the interest in the assessment of ventilation inhomogeneity in infants (Latzin and Thompson 2014). Inhomogeneity indices may be more sensitive than other lung function measures for the early detection of small airway disease in infants and these tests may be easier to perform than conventional lung function tests in this population. Indeed, considerable evidence has shown that, in pediatric patients with cystic fibrosis, LCI is a sensitive, reproducible and practical measure for early detection of small airway dysfunction (Gustafsson et al 2003, Aurora et al 2005a, Belessis et al 2012) and for the assessment of treatment effects (Subbarao et al 2013).
In children older than six years of age, the LCI has a narrow normal range independent of age and height (Lum et al 2013). In younger children, however, the LCI is growth dependent due to structural and functional lung growth in these children (Aurora et al 2005b, Lum et al 2013), and lung volumes, especially airway dead spaces, have a greater effect on the LCI (Habib and Lutchen 1991, Schmalisch et al 2006, Haidopoulou et al 2012). The ratio of dead space to lung volume is greater for face masks used to measure LCI in young infants than for mouthpieces used in older children, adversely affecting gas mixing efficiency. This study was therefore designed to investigate the determinants of LCI in young infants by modeling and by measurements in former preterm infants, of median postmenstrual age 46.7 weeks, previously treated in the neonatal intensive care unit (NICU). This study also compared LCI in wheezing and non-wheezing infants to illustrate the difficulties of LCI interpretation at this age.

Methods

LCI modeling

For an ideal lung model (figure 1) with a uniformly ventilated volume, the washout curve of an inert gas can be expressed as (see appendix):

$$c^n = c_0 \left( \frac{FRC + V_D}{FRC + V_T} \right)^n, \quad n = 0, 1, 2, \ldots, N.$$  \hspace{1cm} (1)

where $c^n$ is the end-expiratory gas concentration of the $n$th breathing cycle, $c_0$ is the initial gas concentration, $V_D$ is the dead space volume without any gas mixing, FRC is the functional residual capacity and $V_T$ is the tidal volume with ideal gas mixing. Using the definition of the LCI

$$\frac{c^{N_{LCI}}}{c_0} = \left[ \frac{FRC + V_D}{FRC + V_T} \right]^{N_{LCI}} \leq \frac{1}{40},$$  \hspace{1cm} (2)

the absolute number of breathing cycles $N_{LCI}$ required to reduce the end-tidal tracer gas concentration to one-fortieth its concentration at the start of wash-in/out can be expressed as:
$$N_{LCI} = \left[ 0.5 + \frac{\log(40)}{\log\left(\frac{FRC + V_T}{FRC + V_D}\right)} \right]$$

Assuming a constant $V_T$, the LCI of the model shown in figure 1 can be expressed as

$$LCI = \frac{N_{LCI} V_T}{FRC}$$

indicating that LCI depends only on three parameters, $V_D$, $V_T$ and FRC.

**Subjects**

This retrospective study evaluated LCI measurements in 150 infants assessed between March 2010 and February 2014 during lung function testing (LFT) as part of our routine follow-up care of infants after removal from the NICU (Schmalisch et al 2013). Infants with congenital heart disease, neuromuscular disease, or thoracic wall deformities were excluded. Ninety of the enrolled infants underwent computerized respiratory sound analysis before LFT.

All parents provided written informed consent before each LFT, and the Institutional Data Safety Committee approved the design of this study.

**LCI measurements**

LCI was measured as part of our routine LFT in clinically stable infants who had no respiratory infections during the 3 weeks preceding the tests. Briefly, prior to testing, body weight and body length (crown to heel) were measured. After a temperature stabilization period of at least 30 min, all devices were calibrated before measurement according to the manufacturers’ guidelines. Sleeping infants were measured in a supine position with the neck in a neutral position and supported by a neck roll. Sleep was induced 15–30 min before measurements by oral administration of chloral hydrate (50 mg kg$^{-1}$).

Respiratory sounds during tidal breathing were analyzed as described previously (Puder et al 2014) using the PulmoTrack$^{\text{®}}$ monitor (Model 2020, KarmelSonix Ltd., Israel), a commercial device designed to detect wheezing. Subsequently, a compliant silicon mask (Infant mask, sizes 2 and 3; Vital Signs Inc., Totowa, NJ, USA) was tightly placed over the nose and mouth of each subject. The effective dead space of the face masks determined by water displacement using a head model were 12 mL and 23.1 mL, respectively. FRC and LCI were measured by multiple breath washout (MBW) with 4% sulfur hexafluoride ($\text{SF}_6$) as a tracer gas using an ultrasonic flow meter (EXHALYZER D, EcoMedics AG, Dürnten, Switzerland) (Wauer et al 2003, Pillow et al 2004). With this sensor the tracer gas concentration is calculated from the measured molar mass signal of the respiratory gases. This requires an internal numerical correction of the raw measurement signal for humidity and temperature using a simulation model (Latzin et al 2007) (see supplementary material at: stacks.iop.org/PM/36/071601/mmedia). The internal dead space of the flowmeter was reduced by dead space reducers (small and medium) to 1.9 mL and 5.4 mL, respectively. Tidal volume was calibrated before the measurements and after exchange of the dead space reducer in accordance with the manufacturer’s instructions. Beside FRC and LCI the acquisition and analysis software (Wbreath vers. 3.19.5.0; Ndd, Zürich, Switzerland) calculated also $V_T$ and $V_D$ to calculate the different lung volume ratios. The effective dead space of the face mask in use was subtracted from the measured FRC to obtain the FRC at the airway opening (Schulzke et al 2008).
Each infant underwent at least three acceptable MBW procedures. Quality criteria for technical acceptability were regular breathing with a visually stable end-expiratory level for at least five breaths and stable inspiratory and expiratory SF6 concentrations before MBW. Measurements were excluded if there was evidence of sighs, air leaks, irregular breathing or incomplete wash-in or washout phases (Hülskamp et al 2009).

An arterialized capillary blood gas sample was taken at the end of the LFT (ABL800 FLEX, Radiometer, Denmark). Heart rate and oxygen saturation were monitored continuously during the LFT by a pulse oximeter (N-200; Nellcor, Hayward, California, USA).

Statistics

Patient characteristics and all measured and calculated data were reported as medians and interquartile ranges (IQR). Gender-specific z-scores of birth weight, body weight and body length at day of measurement were calculated using published national (Voigt et al 1996) and international (Fenton and Kim 2013) reference data. The relationship of LCI to patient characteristics and to lung volumes and derived volume ratios were assessed by Spearman rank order correlation coefficients. A multiple linear regression analysis with backward selection was used to identify the most important influencing factors on LCI. The association between measured LCI and LCI calculated by modeling was determined using linear regression analysis. Bland-Altman analysis was performed to investigate the agreement and bias between the two variables (Bland and Altman 1986). Data in wheezing and non-wheezing infants were compared using the Mann-Whitney U-test. A multivariate analysis of variance (MANOVA) was used to investigate the effect of patient characteristics at birth and at the day of measurements on the differences in LCI between both patient groups. All statistical analyses were performed using Statgraphics Centurion® software (Version 16.0, Statpoint, Inc., Herndon, VA) and MedCalc Software (Vers. 13.3.1, Mariakerke, Belgium). A p-value less than 0.05 was considered statistically significant.

Results

Patient characteristics

Of the 150 infants, 113 (75%) weighed <1500 g at birth, making them very low birth weight (VLBW) infants. LCI and lung volumes were measured at a median (IQR) postmenstrual age of 46.7 (43.4–51.7) weeks, with the infants having a median (IQR) body weight of 4605 (4000–5405) g and a median (IQR) body length of 56 (53–60) cm. A detailed description of the total population (table S1, available at: stacks.iop.org/PM/36/071601/mmedia) and the results of the MBW measurements (table S2, available at: stacks.iop.org/PM/36/071601/mmedia) are given in the supplementary data.

Correlation of LCI with lung volumes

The Spearman rank order correlation coefficients $R_s$ between measured LCI and patient characteristics and the measured lung volumes are shown in table 1. There was only a weak positive correlation between LCI and birth weight ($p = 0.02$), but a stronger positive correlation between LCI and body weight and length at the day of measurement ($p < 0.001$). An even stronger correlation was seen between LCI and the three lung volumes, $V_D$, $V_T$ and FRC, and their ratios. Except for FRC, all volumes and volume ratios showed a strong positive correlation ($p < 0.001$) with measured LCI. The correlation coefficient between LCI and FRC
was negative, but, the association less significant \((p = 0.013)\). Nevertheless, with increasing FRC the LCI decreases. A multivariate regression analysis considering all parameters shown in table 1 confirmed the results of the univariate evaluation (see supplementary data, available at: stacks.iop.org/PM/36/071601/mmedia). Of the 15 included variables only the lung volumes and their volume ratios showed a statistically significant association with the LCI. After a backward stepwise selection only the two volume ratios \(V_T/FRC\) and \(V_D/V_T\) remained in the final model. The coefficient of determination \((R^2)\) of the final model was 78.5%.

Measured LCI showed a strong linear correlation with LCI calculated according to equation (4) named LCI\(_{\text{predicted}}\) (figure 2). The \(R^2\) of the regression model indicates that LCI\(_{\text{predicted}}\) explains 75% of the variability in measured LCI. Although a Bland-Altman plot (figure 3), showing individual within-subject differences for LCI, showed that these differences were randomly distributed, a bias was evident in all measurements. The measured LCI was always higher than LCI\(_{\text{predicted}}\) with a significant mean (95% CI) difference of 0.96 (0.85–1.07).

**Effect of wheezing on LCI**

The effect of wheezing on the LCI was chosen to illustrate the difficulties in interpreting LCI in young infants. Patient characteristics at birth and on the day of measurement showed no statistically significant between group differences (table 2). Median LCI was significantly lower \((p < 0.001)\) in wheezing than in non-wheezing infants (figure 4). A comparison of lung volumes and volume ratios in wheezing and non-wheezing infants showed that FRC was significantly

### Table 1. Correlations of the lung clearance index with patient characteristics, lung volumes and derived parameters.

<table>
<thead>
<tr>
<th>LCI</th>
<th>(R_s)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>0.141</td>
<td>0.085</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>0.191</td>
<td><strong>0.020</strong></td>
</tr>
<tr>
<td>Birth weight (z)-score</td>
<td>0.196</td>
<td><strong>0.017</strong></td>
</tr>
<tr>
<td><strong>At day of measurement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (days)</td>
<td>0.127</td>
<td>0.120</td>
</tr>
<tr>
<td>Postmenstrual age (weeks)</td>
<td>0.215</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>0.391</td>
<td>&lt; <strong>0.001</strong></td>
</tr>
<tr>
<td>Body weight (z)-score</td>
<td>0.198</td>
<td><strong>0.015</strong></td>
</tr>
<tr>
<td>Body length (cm)</td>
<td>0.382</td>
<td>&lt; <strong>0.001</strong></td>
</tr>
<tr>
<td>Body length (z)-score</td>
<td>0.177</td>
<td><strong>0.031</strong></td>
</tr>
<tr>
<td><strong>Lung volumes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(V_D) (mL)</td>
<td>0.782</td>
<td>&lt; <strong>0.001</strong></td>
</tr>
<tr>
<td>(V_T) (mL)</td>
<td>0.444</td>
<td>&lt; <strong>0.001</strong></td>
</tr>
<tr>
<td>FRC (mL)</td>
<td>−0.205</td>
<td></td>
</tr>
<tr>
<td>(V_D/FRC)</td>
<td>0.733</td>
<td><strong>0.013</strong></td>
</tr>
<tr>
<td>(V_T/FRC)</td>
<td>0.854</td>
<td>&lt; <strong>0.001</strong></td>
</tr>
<tr>
<td>(V_D/FRC)</td>
<td>0.688</td>
<td>&lt; <strong>0.001</strong></td>
</tr>
<tr>
<td><strong>Predicted LCI by modeling</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCI(_{\text{predicted}})</td>
<td>0.871</td>
<td>&lt; <strong>0.001</strong></td>
</tr>
</tbody>
</table>

\(R_s\), Spearman rank order correlation coefficient.
higher \( p = 0.001 \) and the volume ratios \( V_D/FRC \) \( p = 0.023 \) and \( V_T/FRC \) \( p = 0.001 \) significantly lower in wheezing infants, which may explain the significant reduction of \( LCI_{\text{predicted}} \) \( p = 0.018 \) in wheezers (table 3).

A multivariate analysis of variance (MANOVA) with the patient characteristics as covariates was performed to investigate the effect of patient characteristics at birth and at the day of measurements on the LCI (see supplementary data, available at: stacks.iop.org/PM/36/071601/mmedia).
There was no statistically significant impact of the covariates, and the LCI remained statistically significant different between wheezers and non-wheezees after adjustment for the patient characteristics ($p = 0.029$). In contrast to the differences in LCI, blood gas concentrations were similar in both patient groups (table 3).

**Table 2.** Patient characteristics of infants without and with expiratory wheezing.

<table>
<thead>
<tr>
<th></th>
<th>Without expiratory wheezing $N = 49$</th>
<th>With expiratory wheezing $N = 41$</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonatal period</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28(57%)</td>
<td>21(51%)</td>
<td>0.574</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>28 (26–32)</td>
<td>28 (26–31)</td>
<td>0.845</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>942 (745–1730)</td>
<td>984 (755–1910)</td>
<td>0.827</td>
</tr>
<tr>
<td>Birth weight z-score</td>
<td>−0.23 (−1.0–0.28)</td>
<td>−0.14 (−0.8–0.37)</td>
<td>0.533</td>
</tr>
<tr>
<td>Birth weight &lt;1000 g</td>
<td>27(55%)</td>
<td>21(51%)</td>
<td>0.712</td>
</tr>
<tr>
<td>Fetal lung maturation</td>
<td>36(73%)</td>
<td>26 (63%)</td>
<td>0.305</td>
</tr>
<tr>
<td>Surfactant administrationa</td>
<td>31(63%)</td>
<td>24/39 (62%)</td>
<td>0.868</td>
</tr>
<tr>
<td>Mechanical ventilation &gt;24 h</td>
<td>26 (53%)</td>
<td>17 (41%)</td>
<td>0.273</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (days)</td>
<td>16.5 (7–38)</td>
<td>13 (6–20)</td>
<td>0.291</td>
</tr>
<tr>
<td><strong>At day of measurement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (days)</td>
<td>149 (100–178)</td>
<td>123 (93–157)</td>
<td>0.156</td>
</tr>
<tr>
<td>Postmenstrual age (weeks)</td>
<td>48.3 (44.1–54.7)</td>
<td>46.3 (42.4–51.4)</td>
<td>0.165</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>4710 (3835–6060)</td>
<td>4585 (3750–5300)</td>
<td>0.315</td>
</tr>
<tr>
<td>Body weight z-score</td>
<td>−0.59 (−1.36–0.19)</td>
<td>−0.25 (−0.92–0.49)</td>
<td>0.193</td>
</tr>
<tr>
<td>Body length (cm)</td>
<td>57 (55–63)</td>
<td>56 (52.5–58)</td>
<td>0.127</td>
</tr>
<tr>
<td>Body length z-score</td>
<td>−0.03 (−1.1–0.44)</td>
<td>0.05 (−1.15–0.71)</td>
<td>0.598</td>
</tr>
</tbody>
</table>

*a Total number is reduced because some data of outpatients were incomplete.

*Note:* data represent median (interquartile range) or $n$ (%).

**Figure 4.** Comparison of LCI in infants without and with expiratory wheezing. The horizontal bar represents the median.
Table 3. Results of MBW measurements in infants without and with expiratory wheezing.

<table>
<thead>
<tr>
<th>MBW measurements</th>
<th>Without expiratory wheezing N = 49</th>
<th>With expiratory wheezing N = 41</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>V_D (mL)</td>
<td>6.05 (3.30–9.60)</td>
<td>4.28 (2.88–8.03)</td>
<td>0.285</td>
</tr>
<tr>
<td>V_D (mL.kg⁻¹)</td>
<td>1.27 (0.91–1.64)</td>
<td>1.02 (0.79–1.67)</td>
<td>0.433</td>
</tr>
<tr>
<td>V_T (mL)</td>
<td>37.7 (27.7–55.8)</td>
<td>32.0 (27.0–43.1)</td>
<td>0.264</td>
</tr>
<tr>
<td>V_T (mL.kg⁻¹)</td>
<td>8.01 (6.47–9.14)</td>
<td>7.27 (6.61–8.66)</td>
<td>0.494</td>
</tr>
<tr>
<td>FRC (mL)</td>
<td>95.9 (77.8–122.1)</td>
<td>116.2 (84.2–147.5)</td>
<td>0.037</td>
</tr>
<tr>
<td>FRC (mL.kg⁻¹)</td>
<td>20.2 (16.2–24.7)</td>
<td>24.3 (20.3–28.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>V_D/V_T</td>
<td>0.16 (0.13–0.21)</td>
<td>0.14 (0.11–0.20)</td>
<td>0.326</td>
</tr>
<tr>
<td>V_D/FRC</td>
<td>0.062 (0.045–0.10)</td>
<td>0.044 (0.031–0.075)</td>
<td>0.023</td>
</tr>
<tr>
<td>V_T/FRC</td>
<td>0.39 (0.33–0.48)</td>
<td>0.32 (0.24–0.36)</td>
<td>0.001</td>
</tr>
<tr>
<td>LCI</td>
<td>6.54 (6.03–7.22)</td>
<td>5.83 (5.45–6.52)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LCIpredicted</td>
<td>5.43 (5.08–5.82)</td>
<td>5.09 (4.79–5.62)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood gases</th>
</tr>
</thead>
<tbody>
<tr>
<td>paO₂ (mmHg)</td>
</tr>
<tr>
<td>paCO₂ (mmHg)</td>
</tr>
</tbody>
</table>

Note: data represent median (interquartile range). Statistically significant values are printed in bold.

Discussion

The results presented here demonstrate that, in young infants, the LCI is highly affected by lung volumes, with about 75% of the changes in LCI predicted by changes in lung volume. These findings indicate that at this age the LCI is of limited value as a measure of the homogeneity of alveolar ventilation. The volume ratios $V_D/FRC$, $V_D/V_T$ and $V_T/FRC$ showed the highest correlation with LCI, indicating that the LCI depends mainly on the tidal volume, the dead space fraction and the ratio of lung volumes with and without gas mixing.

Reductions in dead space volume will improve alveolar ventilation and reduce the number of volume turnovers required to wash out lungs and thus the LCI. This may also be a major effect of most methods of non-invasive ventilatory support (Mahmoud et al 2011) in young infants. For example, the continuous driving flow of a nasal continuous positive airway pressure or high flow nasal cannula device may wash out the oropharyngeal dead space. Despite differences in patient interfaces and applied pressure, no clinically significant differences in the treatment effects of these techniques have been reported to date (Yoder et al 2013). In contrast, any increase in $V_D$, due, for example, to additional apparatus dead space (face mask + flow sensor/gas analyzer) will lead to an increase in LCI. Unfortunately, the equipment used to measure LCI influences the parameters being measured and hampers the ability to compare LCI measurements employing different techniques and equipment.

The observed positive correlation between LCI and body weight and length was unexpected. However, this phenomenon has been reported previously (Schulzke et al 2010). In the present study $LCI_{predicted}$ calculated from the lung volumes showed also a positive correlation with body weight ($R_s = 0.282, p < 0.001$) and body length ($R_s = 0.278, p < 0.001$). Thus, the
increase of the LCI with increasing body weight and length may be caused more by changes in the lung volumes than by an increased ventilation inhomogeneity. Moreover, the patients investigated in our study represent a heterogeneous sample of neonates receiving neonatal intensive care during the first days of life. This heterogeneity of our study population with different patterns of lung function abnormalities could cover the effect of gestational age and body weight on the LCI shown in previous studies (Hulskamp et al. 2009, Schulzke et al. 2010).

Several studies have investigated the dependence of different ventilation inhomogeneity indices on breathing patterns (Edelman et al. 1968, Larsson et al. 1988, Schmalisch et al. 2006). This dependence may be reduced by moment analysis of the washout curve plotted as a function of the cumulative exhaled volume related to the FRC (Saied et al. 1975). However, the calculated moment ratios remained dependent on the dead-space. To reduce the influence of $V_D$, the cumulative exhaled volume was replaced by the cumulative alveolar volume ($V_T - V_D$), with the calculated indices reported as alveolar-based mean dilution numbers (Habib and Lutchen 1991). The same correction was suggested in calculating the LCI (Haidopoulou et al. 2012). However, determining the exact volume of dead space while measuring MBW is often difficult, especially in small lungs, and the resulting high within-subject variability in dead space measurements limits the diagnostic value of these dead-space corrected parameters (Schibler and Henning 2001, Proquitte et al. 2010, Haidopoulou et al. 2012). Furthermore, dead space measurements are highly method-dependent. For example, the airway dead spaces measured with the equipment used in this study were distinctly lower than those measured using volumetric capnography (about 1.8 mL kg$^{-1}$ (Fouzas et al. 2014)).

Most ventilation inhomogeneity indices are abstract mathematical measures calculated from tracer gas washout curves (Pillow et al. 2006), making the LCI one of most frequently used indices of inhomogeneity in infants. The LCI is well defined, easy to measure, is independent of the shape of the washout curve and, most importantly, is easy to comprehend. Increases and decreases in the LCI indicate increases and decreases, respectively, in the number of volume turnovers required to wash out tracer gas from the lungs. Theoretically, the LCI is a static value of the flat tail of the washout curve and may vary if the signal is noisy, explaining its higher within-subject variability than measured FRC (Shao et al. 1998, Schibler and Henning 2001, Schulzke et al. 2008). Thus, accurate measurements require higher numbers of washin and washout cycles for LCI than for FRC.

Modeling showed that, by definition, the LCI was dependent on the lung volume parameters $V_T$, $V_D$ and FRC. This dependence can lead to misleading assessments. A study in ventilated piglets (Proquitte et al. 2006) showed that increasing $V_T$ by increasing peak inspiratory pressure, thereby decreasing dead space fraction, resulted in a mean reduction in the LCI, with this reduction caused exclusively by changes in lung volumes, not by improvements in the homogeneity of alveolar ventilation (Schmalisch et al. 2006). In a clinical study paired SF$_6$ MBW measurements with nasal and face masks were performed in unsedated preterm infants (Schulzke et al. 2008). Despite the lower effective dead space of the nasal mask compared with the face mask (2 mL versus 5 mL), the LCI was significantly higher when using a nasal mask. Infants measured with a nasal mask had also a trend to a lower FRC and a significantly higher $V_D/V_T$ which may explain the higher LCI. Thus, the increased LCI was probably not due to a more ventilation inhomogeneity.

Also, unexpectedly, our results showed that the LCI was lower in wheezing than in non-wheezing infants, whereas there were no differences in concentrations of measured blood gases. Wheezing was likely associated with a functional increase in FRC, a breathing strategy used to increase the end-expiratory lung volume in newborns (Stark et al. 1987, Schmalisch et al. 2003). As $V_D$ and $V_T$ were similar in wheezers and non-wheezers, an increase in FRC...
would result in a decrease in LCI. Therefore, wheezing was unlikely to have had a significant effect on the homogeneity of alveolar ventilation.

**Conclusion**

The availability of commercial equipment has enabled LCI measurements to be easily performed, even in young infants. However, interpretation of the measured LCI at this age must consider its higher dependence on lung volumes. Changes in tidal volume and FRC, or in the apparatus dead space, may affect measured LCI. Model simulations of a uniformly ventilated volume can help to determine whether changes in measured LCI are caused by changes in lung volumes or by changes in the homogeneity of alveolar ventilation.

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**Appendix**

The tracer gas washout curve of an idealized lung model shown in figure 1 can be determined from the end-expiratory tracer gas volume balance, expressed as

\[ c_0(FRC + V_D) = c_{n-1}(FRC + V_D) - (V_T - V_D) \cdot C_n \text{ with } n = 1, \ldots, n. \]

Rearrangement yields a recursive equation to calculate end-expiratory tracer gas concentration

\[ c_n = c_{n-1} \left( \frac{FRC + V_D}{FRC + V_T} \right) \text{ with } n = 1, \ldots, n. \]

which can be transformed by Z-transformation in the geometric series

\[ c^n = c_0 \left[ \frac{FRC + V_D}{FRC + V_T} \right]^n \text{ with } n = 0, 1, 2, \ldots N. \]

The measured FRC$_{\text{meas}}$ is the area under the normalized washout curve, expressed as

\[ \text{FRC}_{\text{meas}} = \frac{1}{c_0} \sum_{n=1}^{\infty} (V_T - V_D) \cdot c_0 \left( \frac{FRC + V_D}{FRC + V_T} \right)^n = (V_T - V_D) \sum_{n=1}^{\infty} \frac{FRC + V_D}{FRC + V_T} \]

Using the sum formula for a geometric series

\[ \text{FRC}_{\text{meas}} = (V_T - V_D) \frac{FRC + V_D}{FRC + V_T} \frac{1}{1 - \frac{FRC + V_D}{FRC + V_T}} = FRC + V_D \]

the measured FRC$_{\text{meas}}$ is always the total volume (FRC + V$_D$) after the gas analyzer in figure 1. Replacement of equation (9) in equation (7) yields an equation for the washout curve

\[ c^n = c_0 \left[ \frac{FRC_{\text{meas}}}{FRC_{\text{meas}} + V_T - V_D} \right]^n, \text{ with } n = 0, 1, 2, \ldots N. \]

an equation derived in 1952 (Fowler et al 1952) for the nitrogen washout technique.
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