Quantitative Assessment of Chronic Lung Disease of Infancy using Computed Tomography

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ABSTRACT

The aims of the study were, to determine if infants and toddlers with Chronic Lung Disease of Infancy (CLDI) have smaller airways and lower lung density compared to full-term healthy controls.

Multi-slice CT chest scans were obtained at elevated lung volumes during a brief respiratory pause in sedated infants and toddlers; 38 CLDI were compared to 39 Controls full-term (FT). For CLDI subjects, gestational age at birth ranged from 25-29 wks. Airway size was measured for trachea and the next 3-4 generations into the right lower lobe; lung volumes and tissue density were also measured.

The relationship between airway size and airway generation differed for CLDI and FT groups; the sizes of the first and second airway generations were larger in the shorter CLDI than the shorter FT subjects. The increased size of the airways in the CLDI subjects was associated with increasing days of mechanical ventilation in the neonatal period. CLDI subjects had a greater heterogeneity of lung density compared to FT subjects.

Our results indicate that quantitative analysis of multi-slice CT scans at elevated volumes provides important insight into the pulmonary pathology of infants and toddlers with CLDI.

Keywords: BPD; Growth and development of the lung; HRCT; lung volume measurement

INTRODUCTION
Modern treatment has lowered the limits of viability for premature birth to less than 25 weeks gestation; however, chronic respiratory sequelae remain a common outcome following extreme premature birth [1-3]. Physiologic assessments of infants with CLDI have demonstrated decreased forced expiratory flows, and decreased pulmonary diffusing capacity, but normal alveolar volumes [4-6]. The limited morphometric data suggests an arrest in alveolar development with fewer and larger alveoli [7]; however, this data has primarily been obtained from autopsy or biopsy data, which most often reflects the most severe disease [8].

Multi-slice Computed Tomography (CT) has been used in lung diseases to assess in vivo lung structure (airway dimensions, tissue density and lung volume), which has improved our understanding of the pulmonary pathophysiology [9-11]. High quality CT images at an elevated lung volume can be obtained in sedated infants, which enable the quantitative assessment of in vivo lung structure [12, 13]. As infants with CLDI have decreased forced expiratory flows [5], we hypothesized they would have smaller sized airways and/or thickened airway walls compared to full-term healthy Controls (FT). In addition, lung tissue density measured by CT is dependent on the relationships between parenchymal tissue and air. Therefore, we also hypothesized that if CLDI subjects had an arrest in alveolar development with fewer but larger alveoli, then CLDI subjects would have lower lung tissue density compared to FT Controls.

METHODS
Subjects

We recruited CLDI subjects from the NICU and outpatient clinics of James Whitcomb Riley Hospital for Children (Indianapolis, IN). We evaluated subjects born between 23-29 weeks gestation, who were clinically stable outpatients without acute respiratory symptoms >3 weeks, and no oxygen requirement. Subjects with a congenital cardio-respiratory disease were excluded.

FT Controls (>37 weeks gestation) were recruited in the Department of Radiology from those scheduled to undergo a non-pulmonary CT scan under sedation for clinical evaluation of a non-respiratory problem. Subjects were excluded for history of recurrent respiratory illness, use of asthma medications, hospitalization for a respiratory illness, or congenital cardio-respiratory abnormalities. Parents consented for the additional non-clinical CT scan of the chest. Results from most FT Controls have been published and data from CLDI subjects has been presented as an abstract [13, 14]. The study was approved by the Institutional Review Board, and parents gave written informed consent.

HRCT Imaging

Multislice volumetric CT images were obtained during an induced respiratory pause at an elevated lung volume, defined by an airway pressure of 20 cmH2O, using a LightSpeed Ultra 16 scanner (GE Healthcare; Milwaukee). Radiation exposure from chest CT imaging was estimated as 4.8 mGy with a low radiation protocol of 120 KV, 20 MAS, 0.625mm collimation thickness, pitch 1.2, and rotation speed 0.5 second. All patients had bismuth shielding to decrease dose to the breast and thyroid. [13] Images were processed using the automated software Pulmonary Workstation 2 (VIDA
diagnostics, Iowa City, USA). Measurements from the trachea (generation 0) and the next 4 airway generations into the right lower lung were analyzed as the pathway with the largest sized airways: right main bronchus (generation 1), bronchus intermedius (generation 2), RLL7 (generation 3) and TriRLL (generation 4). Inner and outer cross-sectional areas (CSA) were measured and wall area was calculated as the difference between these two areas. The lung parenchyma was segmented from the chest wall and the hilar structures, and lung density, tissue weight, and lung and air volumes were calculated [13].

**Classification of CLDI Severity**

CLDI was classified as mild, moderate or severe using NIH criteria based upon the requirements for supplemental oxygen at ≥ 28 days of postnatal age or at ≥36 weeks of postmenstrual age [15]. Days of supplemental oxygen and days of mechanical ventilation were calculated from medical records.

**Statistical Analysis**

Demographic and neonatal characteristics were summarized and compared between FT and CLDI subjects using two-sample t-test or Pearson’s Chi-square test as appropriate. A linear mixed-effect model was used to analyze airway size (inner CSA) on five generations of 16 airways at 5 levels related to the right lower lobe. A full model with main effect, two-way, and three-way interactions of height, generation, and group (CLDI vs. FT) was first fitted. The model adjusted for gender, race, and maternal smoking during pregnancy. If the three-way interactions were not significant at level 0.1, we only kept the two-way interactions with p-value < 0.1. The group effect was
evaluated by generation under the linear-mixed model framework if there was a significant group and generation interaction (Table 2). Similar analysis with height sub-groups as covariate were performed to corroborate the findings; height sub-groups were shorter and taller (respectively ≤ or > than median height). This analysis with grouped height was restricted to subjects with height < 83 cm due to the lack of premature subjects with ≥ 83 cm height. Linear mixed models were also used to evaluate the relationship between neonatal variables and inner CSA. We also fitted the model with three-way interactions for Group Generation, and Height sub-groups, to evaluate the difference between taller and shorter subjects on group effects across generations. Similar analyses were performed for outer CSA and wall area. Interaction terms among generation, group, and neonatal variables were included only if its p-values were < 0.1 (Tables 2, 3).

Lung density was first summarized by its mean, median, coefficient of variation (LDCOV) for each subject. The relationships between the mean, median, LDCOV with neonatal variables were evaluated using linear regression models adjusting for gender, race, maternal smoking during pregnancy and height (Table 4). Total lung volume, tissue volume, and air volume were associated with neonatal variables by linear regression models adjusting for the same set of covariates. All analyses were performed using SAS 9.2.

RESULTS
Subjects

We evaluated 39 CLDI and 41 FT subjects (Table 1). Most of the FT subjects were being clinically evaluated for cranial deformities, hearing loss, or tumors not located in the chest [13]. There were no significant differences between the CLDI and FT groups for distributions for sex, race and maternal smoking during pregnancy; however, CLDI were younger and smaller compared to FT.

Airways

There were significant effects of Generation number and body length on inner CSA, which decreased with increasing generation number from central to peripheral airways and increased with increasing body length (Table 2). There was not a significant isolated Group effect (CLDI vs. Controls); however, there was a significant interaction term for Group by Generation. This interaction of Group by Generation can be illustrated by repeating the above analysis with continuous height replaced by sub-groups of Taller and Shorter subjects based upon the median height for subjects < 83 cm, as there were no CLDI subjects > 83 cm. As illustrated in Figure 1, Control subjects demonstrate a decrease in CSA from central to peripheral generations and a parallel increase in CSA with increasing height from Shorter to Taller subjects. The Shorter and Taller CLDI subjects also exhibit a decrease in CSA with increasing Generation number. However, in contrast to the Controls, these relationships for the Shorter and Taller CLDI subjects are not parallel. Figure 1 also shows inner CSA with the three-way interaction of generation, height sub-groups, and groups (CLDI and FT) to further demonstrate this difference between Shorter and Taller subjects. Among the Shorter subjects, CSA of generations 0 and 1 are significantly larger for CLDI than Control subjects (respectively,
p = 0.036 and p<0.001), while generation 4 has a tendency of having smaller CSA for CLDI than Controls (p=0.14). Among Taller subjects, there were no significant differences in CSA of any generations for CLDI and Control subjects.

We also evaluated whether neonatal factors, such as gestational age and days of mechanical ventilation or supplemental oxygen were associated with inner CSA among CLDI subjects. After adjusting for body length at the time of evaluation, increased CSA was associated with increasing days of mechanical ventilation (p=0.018), as well as increasing days of supplemental oxygen (p=0.026); there was no association with gestational age (p=0.192).

For our overall analysis, we adjusted for sex, race, and maternal smoking during pregnancy, as data from pulmonary function testing has suggested these factors may be important determinants of airway size [16]. Sex was not associated with airway size, while race approached significance with Caucasians tending to have smaller airways compared to Non-Caucasians (p=0.079). Maternal smoking during pregnancy was associated with smaller inner CSA (p=0.036).

The analysis for outer CSA and airway wall CSA demonstrated similar findings as those for inner CSA; the results are summarized in Tables 2 and 3.

**Lung Parenchyma**

**Lung Density**: Sixteen FT subjects received IV contrast for their non-respiratory CT; therefore, we grouped subjects as CLDI, FT without contrast, and FT with contrast. There was an overall significant relationship between lung density and body length; lung density decreased with increasing body length (p<0.001). There were no significant
differences in lung density between CLDI subjects and FT controls without contrast (Figure 2), while FT subjects with contrast had a significantly greater lung density (see on-line supplement).

We evaluated the heterogeneity of density within the lung by calculating the coefficient of variation for lung density ($LD_{COV}$: standard deviation divided by the mean) for each subject. $LD_{COV}$ increased with increasing body length for all groups and was significantly greater for CLDI subjects compared to FT controls without contrast ($p=0.007$) (Figure 3). Among CLDI subjects, lung density nor $LD_{COV}$ were associated with gestational age, days of mechanical ventilation, or supplemental oxygen (Table 4). Sex, race, and maternal smoking during pregnancy had no significant effects for mean lung density. For $LD_{COV}$, race and maternal smoking had no effect, while there was a tendency of females to have a smaller $LD_{COV}$ than males ($p=0.05$).

**Lung Volumes:**

There was an overall significant relationship between lung volumes and body length; total lung volume, air volume and tissue volume all increased with increasing body length ($p<0.001$). Comparing the three groups adjusting for body length, there were no significant differences in total volume, air volume, and tissue volume between CLDI subjects and FT controls without contrast (Figure 4, 5 and 6). FT subjects that had received contrast had significantly greater tissue volume compared to FT subjects that did not receive contrast ($p=0.046$) (see on-line supplement).

Among CLDI subjects, lung, air, and tissue volumes adjusted for body length, had inverse relationships with days of supplemental oxygen; the more days of
supplemental oxygen, the smaller the volumes (Table 4). In addition, lung volume and tissue volume had a direct relationship with gestational age at birth; the greater the gestational age at birth, the larger the lung volumes. Air volume had a similar relationship to gestational age, although it did not achieve statistical significance (p=0.088). Days in mechanical ventilation did not have a significant effect on lung volumes, although there was a tendency for smaller volumes in those who spent more days in mechanical ventilation.

There was a tendency of females to have smaller lung volume and air volume (p=0.07), while Caucasians had significantly greater tissue volume compared to Non-Caucasians (p=0.004), without significant differences for lung and air volume. Maternal smoking during pregnancy was not associated with any of the volumes.

**DISCUSSION**

Our study is the first to use multi-slice CT to obtain a quantitative assessment of lung structure in infants with CLDI who were clinically stable outpatients; previous CT studies used qualitative scores [17-19]. We found important differences and similarities between CLDI and FT subjects in the size of the conducting airways, lung density, and lung volume. The relationship between airway size and airway generation differed for CLDI and FT subjects. The sizes of the first and second airway generations were larger in the shorter CLDI than the shorter FT subjects. The increased airway size in CLDI subjects was associated with increasing days of mechanical ventilation. There were no significant differences in lung volume or mean lung tissue density; however, CLDI subjects had a greater heterogeneity of lung density compared to FT subjects. Our
results indicate that quantitative analysis of multi-slice CT scans provides important insights into the lung structure of infants with CLDI.

In our study, images were obtained during a ventilatory pause at elevated volumes, which provides improved image resolution compared to tidal breathing, particularly in this very young age group that cannot voluntarily perform a breath-hold maneuver [20]. Imaging at elevated lung volumes, closer to total lung capacity rather than to FRC, enables more airway generations to be visualized. In addition, using several inflations and imaging at an elevated lung volume will potentially open peripheral airways that might be closed during tidal breathing, as well as minimize atelectasis that can occur in infants during sedation in the supine position, and thus under-estimate lung volume.

Another major strength of this study was that we had Control data obtained at the same institution with the same methodology. We hypothesized that CLDI subjects would have smaller sized airways and/or increased airway wall thickness when assessed by CT imaging, which might account for decreased forced expiratory flows [4, 5]. We found that the relationship between CSA and airway generation differed for CLDI and FT subjects; however, the first two generations were larger in the shorter CLDI subjects compared to shorter FT subjects. In addition, among the CLDI subjects, increased CSA was associated with increasing days of mechanical ventilation. This finding suggests that the increased CSA of CLDI subjects may have been secondary to repeated mechanical strain produced by mechanical ventilation early in life and more compliant airways, as suggested by animal models [21, 22]. Although the mechanisms for the decreased forced expiratory flows in CLDI infants have not been defined, more
compliant airways could contribute to lower forced expiratory flows. We were not able to obtain quantitative measurements in more peripheral airway generations; therefore, smaller sized peripheral airways could still contribute to lower forced expiratory flows in CLDI.

Reduced forced expiratory flows in otherwise healthy infants have been associated with maternal smoking during pregnancy. [16, 23] Morphometric data from autopsied lungs have reported that maternal smoking during pregnancy was associated with an increased airway wall thickness and increased airway smooth muscle [24]. However, our study is the first to demonstrate that maternal smoking is associated with smaller sized conducting airways among infants and toddlers across both CLDI and FT groups. Our findings suggest that maternal smoking during pregnancy may also be a significant risk factor for increased respiratory disease in infants born prematurely [25].

Morphometric data from autopsied lungs of infants that died with CLDI has demonstrated an arrest in alveolar development with fewer and larger alveoli producing an emphysematous appearance to the lung [26]. Although we hypothesized that CLDI infants would have lower lung density compared to FT controls, we did not find a significant difference. This may reflect that the CLDI subjects we evaluated had significantly less severe parenchymal disease than the reported autopsied CLDI lungs. Alternatively, CT imaging provides a more macroscopic assessment of the lung parenchyma, which may not be sensitive enough to detect milder parenchymal disease, although it has detected emphysematous changes in COPD, as well as anorexia [27, 28]. Our previous study found that the ratio of pulmonary diffusion capacity to lung volume (DL_{CO}/V_A) was significantly lower in CLDI infants compared to FT controls [6].
This finding is consistent with larger, but fewer alveoli; however, a thicker alveolar membrane secondary to increased collagen deposition could also account for lower $DL_{CO}/VA$. We found a greater heterogeneity of lung density for CLDI subjects, which could be related to the lung parenchyma having components that are denser, such as increased collagen, as well as components that are less dense, such as emphysematous changes. Our study is not able to identify the mechanisms for the greater heterogeneity of lung density in the CLDI subjects.

Our assessment of lung volume using CT imaging found no differences between CLDI and FT controls, which is consistent with our previous physiologic findings, as well as other investigators [6, 29]. We did find among the CLDI subjects that the more days of supplemental oxygen the smaller was the lung volume after adjusting for body length. This finding suggests that neonates exposed to more supplemental oxygen and/or those with more severe respiratory disease may have smaller sized lungs. The smaller lung volumes in the CLDI subjects that required more days of supplemental oxygen could be related to decreased lung growth or stiffer, less compliant lungs. Our observed relationship of lung volume and supplemental days of oxygen was present for total lung volume, air and tissue volumes, but not for lung density, which suggests that both the air and tissue components were decreased and consistent with decreased lung growth. We would have expected that increased collagen and stiffer lungs might result in a positive correlation between supplemental oxygen and tissue volume. A few studies of infants with CLDI have reported decreased respiratory system compliance [30]; however, these measurements have been restricted to tidal volume, which can be greatly influenced by airways resistance and airway closure. We are not aware of any
studies that have measured static pressure volume curves for CLDI infants, which would be required to differentiate the effects of lung compliance and lung growth upon lung volume.

Our study had several limitations. First, we only included very premature infants with CLDI; therefore, we cannot distinguish the relative effects of prematurity and CLDI. Future studies require the evaluation of premature infants between 30-36 weeks gestation, as well as extremely premature infants without CLDI. Second, our FT controls cannot be considered completely normal, as they were scheduled for CT scans due to a non-respiratory health problem. However, we excluded subjects with current or past history of respiratory problems. As some FT controls had received IV contrast as part of their clinically scheduled CT, our analysis for the lung parenchyma divided FT subjects into those with and without contrast, which confirmed the effect of intravenous contrast on lung density [31]. Lastly, our assessment of lung growth was limited to cross-sectional data. Longitudinal measurements would provide a better evaluation of growth; however, that would require repeated CT imaging and additional radiation exposure.

In conclusion, we found structural differences in the airways and the lung parenchyma of infants and toddlers with CLDI assessed using multi-slice CT imaging. The relationship between airway size and airway generation differed for CLDI and FT subjects, and CLDI subjects had greater heterogeneity of lung density. Among the CLDI subjects, increasing days of mechanical ventilation was associated with an increased size of more central conducting airways, while increased days of supplemental oxygen was associated with smaller lung volumes.

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We want to thank the following members of the radiology department for their assistance in recruiting patients and performing CT scans: Erv Herman, Brian Towell, Marie Holder, Pamela Monroe, Kathy Steriwart, Mary Beth Miller, Christie Facker, and Shelley Skinner.
Table 1   Demographic and Neonatal Characteristics: CLDI vs Full-term

<table>
<thead>
<tr>
<th></th>
<th>Fullterm</th>
<th>CLDI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>41</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Maternal smoking-pregnancy (yes)</td>
<td>11 (26%)</td>
<td>10 (26%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>25 (60%)</td>
<td>18 (46%)</td>
<td>0.651</td>
</tr>
<tr>
<td>Race (Caucasian)</td>
<td>29 (70%)</td>
<td>25 (64%)</td>
<td>0.635</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.1 (37 to 41)</td>
<td>25.5 (23 to 29)</td>
<td>0.000</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.35 (2.7 to 4.1)</td>
<td>0.87 (0.49 to 1.44)</td>
<td>0.000</td>
</tr>
<tr>
<td>Age (months)</td>
<td>16.7 (4 to 33)</td>
<td>11.9 (5 to 18)</td>
<td>0.002</td>
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<tr>
<td>Weight at test date (Kg)</td>
<td>10.6 (6 to 16)</td>
<td>9.0 (5 to 12)</td>
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</tr>
<tr>
<td>Height at test date (cm)</td>
<td>79.0 (59 to 96)</td>
<td>72.2 (58 to 81)</td>
<td>0.000</td>
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<tr>
<td>Weight/age (Z-score)</td>
<td>0.38 (-2 to 2)</td>
<td>-0.33 (-3 to 2)</td>
<td>0.006</td>
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<tr>
<td>Length/age (Z-score)</td>
<td>0.08 (-2 to 2)</td>
<td>-1.10 (-4 to 1)</td>
<td>0.000</td>
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<tr>
<td>Mechanical ventilation (days)</td>
<td>26.3 (0 to 83)</td>
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<td></td>
</tr>
<tr>
<td>Oxygen (days)</td>
<td>86.2 (28 to 170)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>CPAP (days)</td>
<td>19.0 (0 to 50)</td>
<td>-</td>
<td></td>
</tr>
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</table>

NIH CLDI Severity

<p>| | |</p>
<table>
<thead>
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<tbody>
<tr>
<td>Mild</td>
<td>11(28%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Severe</td>
<td>23 (59%)</td>
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</table>

Data are presented as mean (range), unless otherwise stated.

CLDI= Chronic Lung Disease of Infancy; CPAP=Continuous Positive Airway Pressure
<table>
<thead>
<tr>
<th>Effect</th>
<th>Inner CSA</th>
<th>Estimate</th>
<th>SE</th>
<th>p value</th>
<th>Outer CSA</th>
<th>Estimate</th>
<th>SE</th>
<th>p value</th>
<th>Wall CSA</th>
<th>Estimate</th>
<th>SE</th>
<th>p value</th>
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<tr>
<td>Sex</td>
<td></td>
<td>0.0146</td>
<td>0.0130</td>
<td>0.266</td>
<td></td>
<td>0.0065</td>
<td>0.0109</td>
<td>0.551</td>
<td></td>
<td>0.0031</td>
<td>0.0013</td>
<td>0.804</td>
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<td>Race</td>
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<td>-0.0241</td>
<td>0.01354</td>
<td>0.079</td>
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<td>0.0007</td>
<td>0.0114</td>
<td>0.948</td>
<td></td>
<td>0.0065</td>
<td>0.0132</td>
<td>0.622</td>
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<td>Pregnancy smoking</td>
<td></td>
<td>-0.0306</td>
<td>0.01437</td>
<td>0.036</td>
<td></td>
<td>-0.0261</td>
<td>0.0121</td>
<td>0.034</td>
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<td>Generation 1*</td>
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<td>-0.1616</td>
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<td>0.0117</td>
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<td>Generation 2*</td>
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<td>-0.3467</td>
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<td>-0.1764</td>
<td>0.0109</td>
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<tr>
<td>Generation 3*</td>
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<td>-0.5227</td>
<td>0.01801</td>
<td>&lt;.0001</td>
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<td>-0.4299</td>
<td>0.0131</td>
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<td>-0.294</td>
<td>0.0125</td>
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<tr>
<td>Generation 4*</td>
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<td>-0.6028</td>
<td>0.0169</td>
<td>&lt;.0001</td>
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<tr>
<td>Premature</td>
<td></td>
<td>0.0345</td>
<td>0.0157</td>
<td>0.260</td>
<td></td>
<td>-0.0308</td>
<td>0.0137</td>
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<td>-0.0194</td>
<td>0.0191</td>
<td>0.313</td>
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<tr>
<td>GEN1<em>Premature</em></td>
<td></td>
<td>0.0393</td>
<td>0.0200</td>
<td>0.053</td>
<td></td>
<td>-0.0166</td>
<td>0.0164</td>
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<td>-0.0268</td>
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<td>0.0020</td>
<td>0.0198</td>
<td>0.918</td>
<td></td>
<td>0.0009</td>
<td>0.0145</td>
<td>0.949</td>
<td></td>
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<td>0.0182</td>
<td>0.715</td>
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<td>-0.0534</td>
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<td></td>
<td>0.0474</td>
<td>0.0183</td>
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<td></td>
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<td>0.0252</td>
<td>0.007</td>
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<td>0.049</td>
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<td>0.0047</td>
<td></td>
<td>0.0398</td>
<td>0.0194</td>
<td>0.045</td>
</tr>
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</table>

CSA= Cross-sectional area; CLDI= Chronic Lung Disease of Infancy; GEN=generation;
* In these analysis, Generation 0 (Trachea) is the reference.
Table 3. Relationship between Airway size and neonatal variables in the CLDI group.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Days of Mechanical Ventilation</th>
<th>Days of Supplemental Oxygen</th>
<th>Weeks of Gestational Age at Birth</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
<td>p-value</td>
</tr>
<tr>
<td>Inner CSA (mm²)</td>
<td>0.00096</td>
<td>0.0004</td>
<td>0.017</td>
</tr>
<tr>
<td>Outer CSA (mm²)</td>
<td>0.00068</td>
<td>0.0003</td>
<td>0.029</td>
</tr>
<tr>
<td>Wall CSA (mm²)</td>
<td>0.0005</td>
<td>0.0003</td>
<td>0.062</td>
</tr>
</tbody>
</table>

CSA= Cross-sectional area; CLDI= Chronic Lung Disease of Infancy
Table 4. Relationships of lung parenchyma outcomes and neonatal variables for CLDI group.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Days of Mechanical Ventilation</th>
<th>Days of Supplemental Oxygen</th>
<th>Gestational Age at Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>SE</td>
<td>p-value</td>
</tr>
<tr>
<td>Lung Density (g/cm³)</td>
<td>0.0000</td>
<td>0.0002</td>
<td>0.930</td>
</tr>
<tr>
<td>LD&lt;sub&gt;cov&lt;/sub&gt;</td>
<td>0.0436</td>
<td>0.041</td>
<td>0.296</td>
</tr>
<tr>
<td>Lung Volume (cm³)</td>
<td>-0.102</td>
<td>0.2725</td>
<td>0.707</td>
</tr>
<tr>
<td>Tissue Volume (cm³)</td>
<td>-0.039</td>
<td>0.0245</td>
<td>0.111</td>
</tr>
<tr>
<td>Air Volume (cm³)</td>
<td>-0.063</td>
<td>0.2662</td>
<td>0.813</td>
</tr>
</tbody>
</table>

LD<sub>cov</sub>= Lung Density Coefficient of Variation. CLDI= Chronic Lung Disease of Infancy
Figure 1. CLDI and full-term controls log-transformed inner cross-sectional area by airway generation with Standard Error. Cross-sectional area decreases with each generation going into the right lower lobe. Figure also depicts the interaction term between group and generation. CLDI= Chronic Lung Disease of Infancy; RMB=Right main bronchus; BI= bronchus intermedius, RLL7 and TriRLL.

Figure 2. Lung Density versus body length. As body length increases, lung density decreases in both groups. Fullterm subjects that used IV contrast are not included. CLDI= Chronic Lung Disease of Infancy
Figure 3. Heterogeneity of lung density, expressed as Coefficient of variation ($LD_{cov}$), versus body length. The coefficient of variation increases with increasing height in both groups with the CLDI having higher values. Fullterm that used IV contrast are not included. CLDI= Chronic Lung Disease of Infancy
Figure 4. Total lung volume (ml) versus body length (cm). Total volume increases with increasing body length for both CLDI and FT without IV contrast. There was no significant difference in air volume for CLDI and FT without IV contrast. CLDI= Chronic Lung Disease of Infancy

Figure 5. Air volume (ml) versus body length (cm). Air volume increases with increasing body length for both CLDI and FT without IV contrast. There was no significant difference in air volume for CLDI and FT without IV contrast. CLDI= Chronic Lung Disease of Infancy
Figure 6.  Tissue volume (ml) versus body length (cm). Tissue volume increases with increasing body length for both CLDI and FT without IV contrast. There was no significant difference in tissue volume for CLDI and FT without IV contrast. CLDI= Chronic Lung Disease of Infancy
References


