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Quantitative assessment of chronic lung disease of infancy using computed tomography

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Abstract

The aims of this study were to determine whether infants and toddlers with chronic lung disease of infancy (CLDI) have smaller airways and lower lung density compared with full-term healthy controls.

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

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

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

Keywords

Bronchopulmonary dysplasia; high-resolution computed tomography; lung development; lung volume measurement

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STATEMENT OF INTEREST

None declared.

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Modern treatment has lowered the limits of viability for premature birth to <25 weeks gestation; however, chronic respiratory sequelae remain a common outcome following extremely premature birth [1–3]. Physiological assessments of infants with chronic lung disease of infancy (CLDI) have demonstrated decreased forced expiratory flows and 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, these data have primarily been obtained from autopsy or biopsy, which most often reflect 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 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 hypothesised that they would have smaller-sized airways and/or thickened airway walls compared with full-term healthy controls. In addition, lung tissue density measured by CT is dependent on the relationships between parenchymal tissue and air. Therefore, we also hypothesised that if CLDI subjects have an arrest in alveolar development with fewer but larger alveoli, then CLDI subjects would have lower lung tissue density compared with full-term controls.

METHODS

Subjects

We recruited CLDI subjects from the neonatal intensive care unit and outpatient clinics of James Whitcomb Riley Hospital for Children (Indian-apolis, IN, USA). We evaluated subjects born between 23 and 29 weeks' gestation, who were clinically stable outpatients without acute respiratory symptoms >3 weeks and had no oxygen requirement. Subjects with a congenital cardiorespiratory disease were excluded.

Full-term controls (>37 weeks' gestation) were recruited in the Dept of Radiology (James Whitcomb Riley Hospital for Children) from those scheduled to undergo a nonpulmonary 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, hospitalisation for a respiratory illness or congenital cardiorespiratory abnormalities. Parental consent was obtained for the additional nonclinical CT scan of the chest. The results from most full-term controls have been published and data from CLDI subjects have been presented as an abstract [13, 14]. The study was approved by the institutional review board (Indiana University, Indianapolis, IN, USA) and parents gave written informed consent.

High-resolution CT imaging

Multi-slice volumetric CT images were obtained during an induced respiratory pause at an elevated lung volume, defined by an airway pressure of 20 cm H_2O, using a LightSpeed Ultra 16 scanner (GE Healthcare, Milwaukee, WI, USA). Radiation exposure from chest CT

imaging was estimated as 4.8 mGy with a low radiation protocol of 120 kV, 20 $mA{\cdot}s_{effective}$, 0.625 mm collimation thickness, pitch 1.2 and rotation speed 0.5 s. All patients had bismuth shielding to decrease the radiation dose to the breast and thyroid [13]. Images were processed using the automated software Pulmonary Workstation 2 (VIDA diagnostics, Iowa City, IA, USA). Measurements from the trachea (generation 0) and the next four airway generations into the right lower lung were analysed as the pathway with the largest sized airways: right main bronchus (generation one), bronchus intermedius (generation two), RLL7 (generation three) and TriRLL (generation four). Inner and outer cross-sectional areas 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 National Institutes of Health criteria based upon the requirements for supplemental oxygen at ≥28 days post-natal age or at ≥36 weeks post-menstrual age [15]. Days of supplemental oxygen and days of mechanical ventilation were calculated from medical records.

Statistical analysis

Demographic and neonatal characteristics were summarised and compared between full-term and CLDI subjects using a two-sample unpaired t-test or Pearson's Chi-squared test, as appropriate. A linear mixed-effect model was used to analyse airway size (inner cross-sectional area) on five generations of 16 airways at five 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 *versus* full-term) was fitted first. The model was adjusted for sex, 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 1). Similar analysis with height sub-groups as covariates were performed to corroborate the findings; height sub-groups were shorter and taller (less than or equal to or greater than median height, respectively). This analysis with grouped height was restricted to subjects with height <83 cm due to the lack of premature subjects with height ≥83 cm. Linear mixed models were also used to evaluate the relationship between neonatal variables and inner cross-sectional area. 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 cross-sectional area and wall area. Interaction terms among generation, group and neonatal variables were included only if p-values were <0.1 (tables 1 and 2).

Lung density was first summarised by its mean, median and coefficient of variation (LD_{COV}; standard deviation divided by the mean) for each subject. The relationships between the mean, median and LD_{COV} with neonatal variables were evaluated using linear regression models adjusted for sex, race, maternal smoking during pregnancy and height (table 3). 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 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Subjects

We evaluated 39 CLDI and 41 full-term subjects (table 4). Most of the full-term subjects were being clinically evaluated for cranial deformities, hearing loss or tumours not located in the chest [13]. There were no significant differences between the CLDI and full-term groups for distributions for sex, race and maternal smoking during pregnancy; however, CLDI subjects were younger and smaller compared with full-term subjects.

Airways

There were significant effects of generation number and body length on inner cross-sectional area, which decreased with increasing generation number from central to peripheral airways and increased with increasing body length (table 1). There was not a significant isolated group effect (CLDI *versus* controls); however, there was a significant interaction term for group by generation. This interaction of group by generation can be illustrated by repeating the 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 cross-sectional area from central to peripheral generations and a parallel increase in cross-sectional area with increasing height from shorter to taller subjects. The shorter and taller CLDI subjects also exhibit a decrease in cross-sectional area 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 cross-sectional area with the three-way interaction of generation, height sub-groups and groups (CLDI and full-term) to further demonstrate this difference between shorter and taller subjects. Among the shorter subjects, cross-sectional area of generations 0 and one are significantly larger for CLDI than control subjects ($p=0.036$ and $p<0.001$, respectively), while generation four has a tendency of having a smaller cross-sectional area for CLDI than controls ($p=0.14$). Among taller subjects, there were no significant differences in cross-sectional area of any generation 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 cross-sectional area among CLDI subjects. After adjusting for body length at the time of evaluation, increased cross-sectional area 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 with non-Caucasians (p=0.079). Maternal smoking during pregnancy was associated with a smaller inner cross-sectional area (p=0.036).

The analysis of outer cross-sectional area and airway wall cross-sectional area demonstrated similar findings as those for inner cross-sectional area; the results are summarised in tables 1 and 2.

Lung parenchyma

Lung density—16 full-term subjects received intravenous contrast for their non-respiratory CT; therefore, we grouped subjects as CLDI, full-term without contrast and full-term 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 full-term controls without contrast (fig. 2), while full-term subjects with contrast had a significantly greater lung density (see the online supplementary material).

We evaluated the heterogeneity of density within the lung by calculating the LD_{COV} for each subject. LD_{COV} increased with increasing body length for all groups and was significantly greater for CLDI subjects compared with full-term controls without contrast (p=0.007) (fig. 3). Among CLDI subjects, neither lung density nor LD_{COV} were associated with gestational age, days of mechanical ventilation or supplemental oxygen (table 3). Sex, race and maternal smoking during pregnancy had no significant effects on mean lung density. For LD_{COV}, race and maternal smoking had no effect, while there was a tendency for 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 full-term controls without contrast (figs 4, 5 and 6). Full-term subjects who had received contrast for their non-respiratory CT had significantly greater tissue volume compared with full-term subjects that did not receive contrast (p=0.046) (see the online supplementary material).

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 3). 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 of 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 for females to have smaller lung volume and air volume (p=0.07), while Caucasians had significantly greater tissue volume compared with 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 full-term 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 full-term subjects. The sizes of the first and second airway generations were larger in the shorter CLDI than in the shorter full-term 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 with full-term 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 with tidal breathing, particularly in this very young age group that cannot voluntarily perform a breath-hold manoeuvre [20]. Imaging at elevated lung volumes, closer to total lung capacity than to functional residual capacity, enables more airway generations to be visualised. 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 minimise the atelectasis that can occur in infants during sedation in the supine position, and thus underestimate lung volume.

Another major strength of this study was that we had control data obtained at the same institution with the same methodology. We hypothesised 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 cross-sectional area and airway generation differed between CLDI and full-term subjects; however, the first two generations were larger in the shorter CLDI subjects compared with the shorter full-term subjects. In addition, among the CLDI subjects, increased cross-sectional area was associated with increasing days of mechanical ventilation. This finding suggests that the increased cross-sectional area 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 full-term 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 have demonstrated an arrest in alveolar development with fewer and larger alveoli producing an emphysematous appearance to the lung [26]. Although we hypothesised that CLDI infants would have lower lung density compared with full-term 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 chronic obstructive pulmonary disease and anorexia nervosa [27, 28]. Our previous study found that the diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$)/alveolar volume (V_A) ratio was significantly lower in CLDI infants compared with full-term 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 $D_{L,CO}/V_A$. 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 full-term controls, which is consistent with our previous physiological findings, as well as those of other investigators [6, 29]. We did find among the CLDI subjects that the more days of supplemental oxygen, the smaller 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 with days of supplemental 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 airway 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 and 36 weeks' gestation, as well as extremely premature infants without CLDI. Secondly, our full-term 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 full-term controls had received intravenous contrast as part of their clinically scheduled CT, our analysis for the lung parenchyma divided full-term 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 full-term subjects, and CLDI subjects had greater heterogeneity of lung density. Among the CLDI subjects, increasing days of mechanical ventilation were associated with an increased size of the more central conducting airways, while increased days of supplemental oxygen were associated with smaller lung volumes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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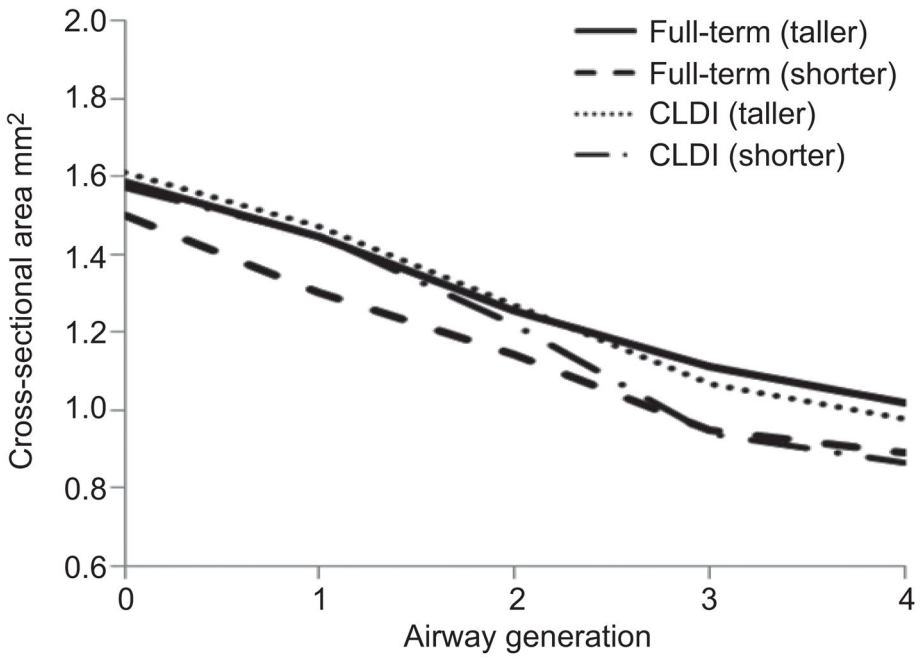

FIGURE 1.

Log-transformed inner cross-sectional area by airway generation for chronic lung disease of infancy (CLDI) cases and full-term controls. Cross-sectional area decreases with each generation going into the right lower lobe. The generations are as follows: trachea (generation 0), right main bronchus (generation one), bronchus intermedius (generation two), RLL7 (generation three) and TriRLL (generation four).

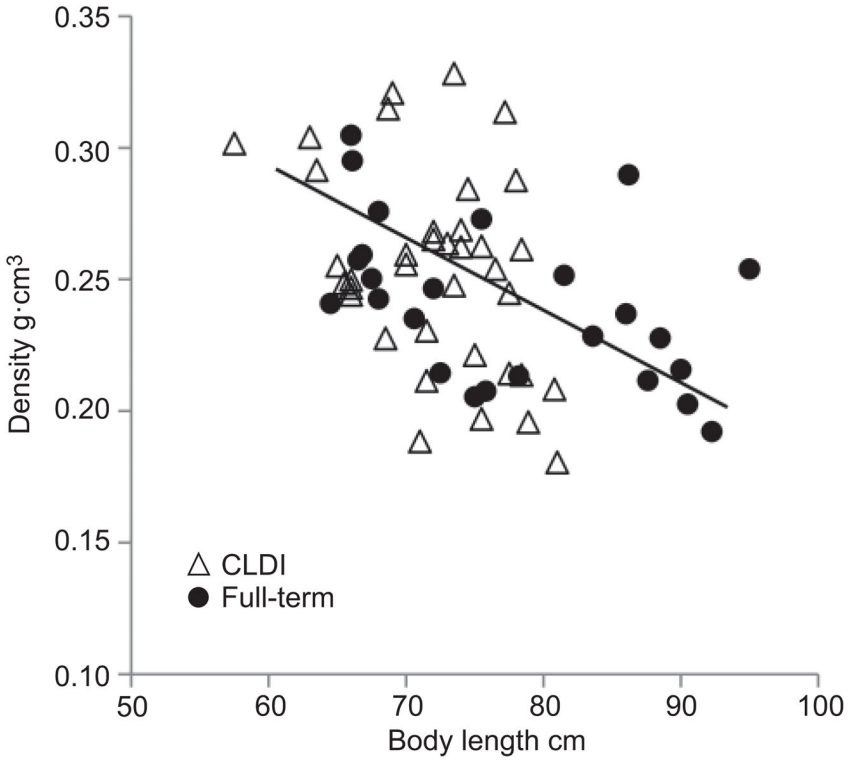

FIGURE 2.

Lung density *versus* body length. As body length increased, lung density decreased in both groups. Full-term subjects who received intravenous contrast were not included. CLDI: chronic lung disease of infancy.

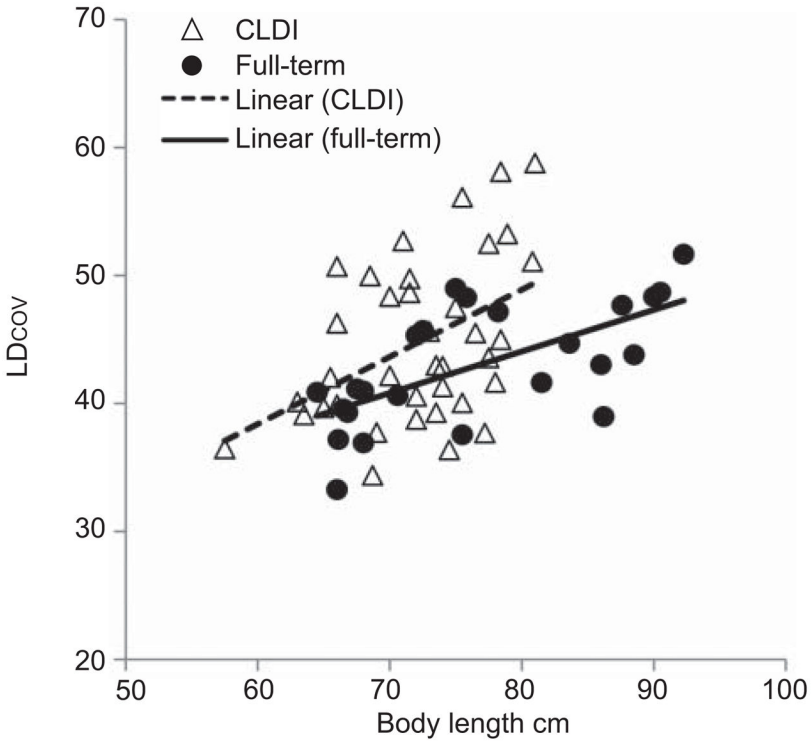

FIGURE 3.

Heterogeneity of lung density coefficient of variation (LD_{COV}) *versus* body length. LD_{COV} increased with increasing height in both groups, with the chronic lung disease of infancy (CLDI) group having higher values. Full-term subjects who received intravenous contrast were not included.

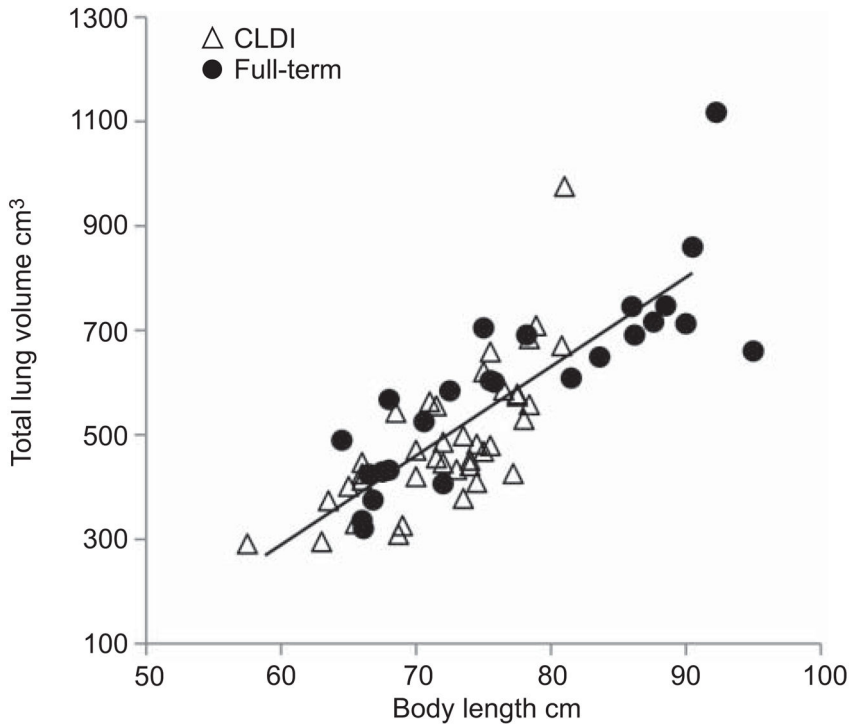

FIGURE 4.

Total lung volume *versus* body length. Total volume increased with increasing body length for both chronic lung disease of infancy (CLDI) and full-term without intravenous contrast subjects. There was no significant difference in air volume for CLDI and full-term subjects without intravenous contrast.

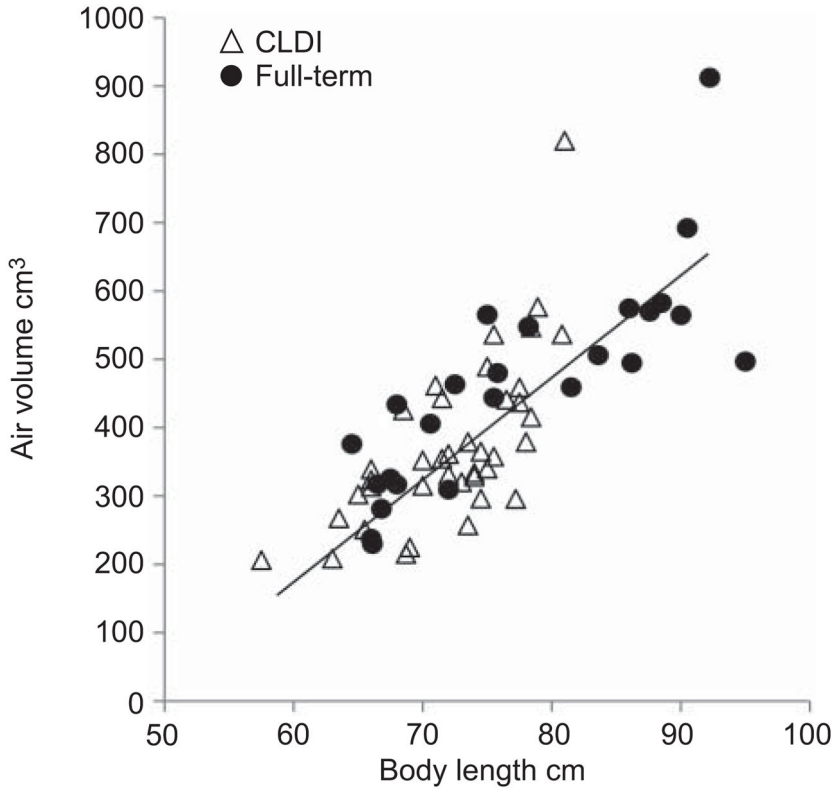

FIGURE 5.

Air volume *versus* body length. Air volume increased with increasing body length for both chronic lung disease of infancy (CLDI) and full-term without intravenous contrast. There was no significant difference in air volume for CLDI and full-term without intravenous contrast.

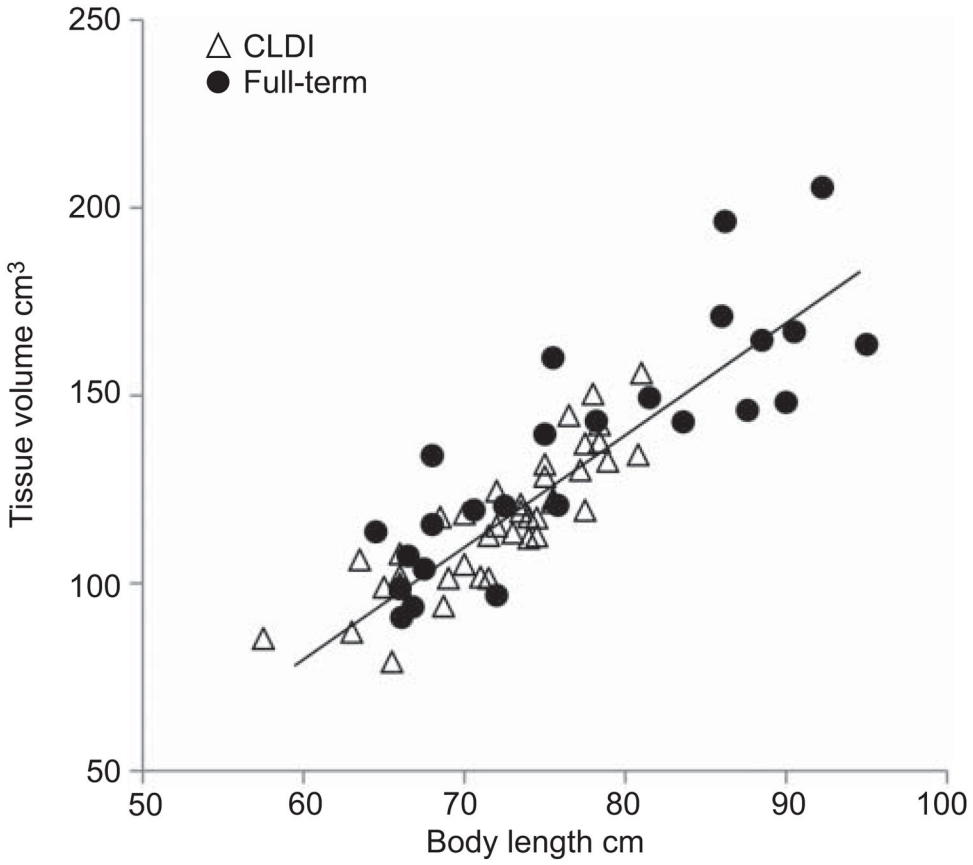

FIGURE 6.

Tissue volume *versus* body length. Tissue volume increased with increasing body length for both chronic lung disease of infancy (CLDI) and full-term without intravenous contrast. There was no significant difference in tissue volume for CLDI and full-term without intravenous contrast.

TABLE 1

Analysis for inner, outer and wall cross-sectional areas (CSAs)

Effect	Inner CSA		Outer CSA		Wall CSA	
	Mean estimate±SE	p-value	Mean estimate±SE	p-value	Mean estimate±SE	p-value
Sex	0.0146±0.0130	0.266	0.0065±0.0109	0.551	0.0031±0.0013	0.804
Race	−0.0241±0.01354	0.079	0.0007±0.0114	0.948	0.0065±0.0132	0.622
Smoking during pregnancy	−0.0306±0.01437	0.036	−0.0261±0.0121	0.034	−0.0290±0.0140	0.042
Gen 1[#]	−0.1616±0.01344	<0.0001	−0.1018±0.0117	<0.0001	−0.0673±0.0126	<0.001
Gen 2[#]	−0.3467±0.01333	<0.0001	−0.2622±0.0104	<0.0001	−0.1764±0.0109	<0.001
Gen 3[#]	−0.5227±0.01801	<0.0001	−0.4299±0.0131	<0.0001	−0.294±0.0125	<0.001
Gen 4[#]	−0.6028±0.0169	<0.0001	−0.4997±0.0120	<0.0001	−0.3356±0.011	<0.001
Premature	0.0345±0.0157	0.260	−0.0308±0.0137	0.250	−0.0194±0.0191	0.313
Gen 1×Premature[#]	0.0393±0.0200	0.053	−0.0166±0.0164	0.312	−0.0268±0.0210	0.207
Gen 2×Premature[#]	0.0020±0.0198	0.918	0.0009±0.0145	0.949	−0.0066±0.0182	0.715
Gen 3×Premature[#]	−0.0534±0.0268	0.050	0.0474±0.0183	0.012	0.0306±0.0208	0.147
Gen 4×Premature[#]	−0.0694±0.0252	0.007	0.049±0.0168	0.0047	0.0398±0.0194	0.045

Gen: generation.

[#]in these analyses, generation 0 (trachea) is the reference.

TABLE 2

Relationship between airway size and neonatal variables in the chronic lung disease of infancy group

	Days of mechanical ventilation		Days of supplemental oxygen		Weeks of gestational age at birth	
	Mean estimate±SE	**p-value**	**Mean estimate±SE**	**p-value**	**Mean estimate±SE**	**p-value**
Inner CSA mm^2	0.00096±0.0004	0.017	0.00057±0.0003	0.026	−0.00777±0.0058	0.191
Outer CSA mm^2	0.00068±0.0003	0.029	0.0004±0.0002	0.047	−0.0035±0.0046	0.447
Wall CSA mm^2	0.0005±0.0003	0.062	0.0002±0.0002	0.106	−0.0012±0.0039	0.752

CSA: cross-sectional area.

TABLE 3

Relationships of lung parenchyma outcomes and neonatal variables for the chronic lung disease of infancy group

	Days of mechanical ventilation		Days of supplemental oxygen		Gestational age at birth	
	Mean estimate±SE	**p-value**	**Mean estimate±SE**	**p-value**	**Mean estimate±SE**	**p-value**
Lung density g·cm^{-3}	0.0000±0.0002	0.930	0.0001±0.0001	0.491	0.0013±0.0038	0.726
LD$_{COV}$	0.0436±0.041	0.296	0.0033±0.0266	0.902	−0.4290±0.6014	0.481
Lung volume cm^3	−0.102±0.2725	0.707	−0.464±0.1699	0.007	8.548±3.8905	0.029
Tissue volume cm^3	−0.039±0.0245	0.111	−0.041±0.0153	0.008	1.991±0.3251	<0.001
Air volume cm^3	−0.063±0.2662	0.813	−0.423±0.1663	0.012	6.557±3.8184	0.088

LD$_{COV}$: lung density coefficient of variation.

TABLE 4

Demographic and neonatal characteristics

	Full-term	CLDI	p-value
Subjects n	41	39	
Maternal smoking during pregnancy	11 (27)	10 (26)	1.00
Females	25 (61)	18 (46)	0.651
Caucasians	29 (71)	25 (64)	0.635
Gestational age weeks	39.1 (37–41)	25.5 (23–29)	0.000
Birth weight kg	3.35 (2.7–4.1)	0.87 (0.49–1.44)	0.000
Age months	16.7 (4–33)	11.9 (5–18)	0.002
Weight at test date Kg	10.6 (6–16)	9.0 (5–12)	0.002
Height at test date cm	79.0 (59–96)	72.2 (58–81)	0.000
Weight/age Z-score	0.38 (−2–2)	−0.33 (−3–2)	0.006
Length/age Z-score	0.08 (−2–2)	−1.10 (−4–1)	0.000
Mechanical ventilation days		26.3 (0–83)	
Oxygen days		86.2 (28–170)	
CPAP days		19.0 (0–50)	
NIH CLDI severity			
Mild		11(28)	
Moderate		5 (13)	
Severe		23 (59)	

Data are presented as n (%) or mean (range), unless otherwise stated. CLDI: chronic lung disease of infancy; CPAP: continuous positive airway pressure; NIH: National Institutes of Health.