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Ventilation Homogeneity Improves with Growth Early in Life

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Abstract

Some studies have suggested that lung clearance index (LCI) is age-independent among healthy subjects early in life, which implies that ventilation distribution does not vary with growth. However, other studies of older children and adolescents suggest that ventilation becomes more homogenous with somatic growth.

We describe a new technique to obtain multiple breath washout (MBWO) in sedated infants and toddlers using slow augmented inflation breaths that yields an assessment of LCI and the slope of phase III, which is another index of ventilation inhomogeneity. We evaluated whether ventilation becomes more homogenous with increasing age early in life, and whether infants with chronic lung disease of infancy (CLDI) have increased ventilation inhomogeneity relative to full term controls.

Fullterm controls (N = 28) and CLDI (N = 22) subjects between 3 and 28 months corrected-age were evaluated. LCI decreased with increasing age; however, there was no significant difference between the two groups (9.3 vs. 9.5; p = 0.56). Phase III slopes adjusted for expired volume (S_{ND}) increased with increasing breath number during the washout and decreased with increasing age. There was no significant difference in S_{ND} between fullterm and CLDI subjects (211 vs. 218; P = 0.77).

Our findings indicate that ventilation becomes more homogenous with lung growth and maturation early in life; however, there is no evidence that ventilation inhomogeneity is a significant component of the pulmonary pathophysiology of CLDI.

Keywords

lung function tests; bronchopulmonary dysplasia; infant; premature; lung clearance index; phase III slope; chronic lung disease of infancy

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INTRODUCTION

Ventilation inhomogeneity is most often assessed in infants and toddlers by calculating the lung clearance index (LCI) from multi-breath inert gas washout (MBWO) during tidal breathing. Most, but not all studies have suggested that LCI is age-independent among healthy subjects early in life, which would have the advantage of a fixed cut-off for detecting airway dysfunction¹⁻⁵. A constant LCI would also suggest that ventilation distribution does not vary with growth and lung development. However, several studies in children have suggested that ventilation does become more homogenous with increasing age⁶⁻⁹.

Measurement of LCI during tidal breathing in sedated, supine infants and toddlers, who are at risk for developing airway closure and atelectasis, may not adequately assess maturational changes in ventilation inhomogeneity in this age group¹⁰. In addition, the decline in respiratory rate with increasing age early in life makes it difficult to compare subjects of differing ages. In adults, the MBWO is often performed with a larger than normal tidal volume and a slow respiratory rate, which standardizes the washout^{11,12}. In addition, using this strategy, phase III slopes (S_{III}) can be assessed and provide additional insights into pulmonary physiology^{11,13-16}. Other than Ream and colleagues, who evaluated anesthetized and ventilated subjects using CO₂ expirograms⁶, S_{III} has not been reported for infants and toddlers secondary to their more rapid respiratory rates and smaller spontaneous tidal volumes that most often prevent the clear identification of S_{III} in this very young age group.

In our current study, we describe a modified MBWO technique in sedated infants and toddlers using augmented inflation breaths, which are much larger than spontaneous tidal volumes. This approach provides a standardized pattern of ventilation with a slow rate and large volume with a clear identification of S_{III} , and the measurement of LCI. We hypothesized that the lung ventilation becomes more homogenous with growth and development early in life, which would be evidenced by a decline of LCI and S_{III} . In addition, we hypothesized that infants and toddlers with chronic lung disease of infancy (CLDI) would exhibit higher values of LCI and S_{III} compared to fullterm controls, which would indicate greater ventilation inhomogeneity.

MATERIALS AND METHODS

Subjects

Fullterm control (FT) infants and toddlers were born at more than 37 weeks gestation and they were recruited by advertisement in local media. Exclusion criteria included hospitalization for respiratory illness, history of asthma, wheezing or treatment with asthma medications or congenital cardio-pulmonary disease. Infants and toddlers with CLDI were recruited from the Newborn Intensive Care Unit and from the follow-up outpatient clinic of James Whitcomb Riley Hospital for Children. Subjects were born at less than 30 weeks of gestational age and were evaluated when clinically stable outpatients with no oxygen requirement at the time of testing. All CLDI subjects had a diagnosis of bronchopulmonary dysplasia, defined as an oxygen requirement at 36 weeks of gestation.¹⁷ Subjects were excluded for congenital cardio-respiratory disease. All subjects were evaluated when free of any acute respiratory symptoms for more than 3 weeks. Tests were performed at the Infant Pulmonary Function Laboratory between 2007 and 2010. The study was approved by the Institutional Review Board of Indiana University and written parental consent was obtained prior to testing.

Multiple Augmented Inflation Breath Inert Gas Washout

Subjects' weight and length were measured and infants were sedated with chloral hydrate (50–100 mg/kg, p.o.) while heart and respiratory rates and oxygen saturation were continuously monitored. Subjects were evaluated in the supine position while breathing through a facemask connected to the circuit, which was a modification of our previously described equipment used to measure forced expiratory flows and pulmonary diffusing capacity from elevated lung volumes^{18,19}, as illustrated in Figure 1. A heated pneumotachometer (3500/4500 series, Hans Rudolph, Shawnee, Kansas) was calibrated with room air using a precision 500 ml syringe. Gas concentration was measured using a mass spectrometer (Perkin Elmer, MGA 1100, Waltham, Massachusetts), which was calibrated daily with certified gases. Flow, airway pressure and He concentration were sampled at a frequency of 100 Hz, and volume was obtained by digital integration of the flow signal. Flow, volume and helium (He) concentration signals were synchronized using software developed by our laboratory; the reference point for alignment was the rapid rise of the pressure signal at the beginning of the augmented inflation breaths.

By spontaneous tidal breathing in the open circuit, subjects equilibrated with the 4% He test gas, as evidenced by the end-expired gas concentration (Figure 2). Then, two augmented inflation breaths were delivered with the same test gas by occluding the expiratory valve in the circuit, which directed the bias flow of test gas to the subject. The augmented inflation breath continued until airway pressure reached 20 cm H₂O and flow reached zero; then, the expiratory valve was opened and passive expiration proceeded to functional residual capacity. During the expiratory phase of the second augmented inflation breath, the inspiratory gas mixture was switched from the He test gas to room air and the washout began and continued with augmented inflation breaths of room air until the end-expiratory He concentration reached 1/40th of the initial concentration. Tidal breathing was only used during the wash-in phase, while the washout phase was performed only with augmented inflation breaths. For each subject, washout measurements were repeated at least twice.

Calculations

The amount of expired He was calculated by integrating the product of gas concentration and flow, adjusting for re-breathed He²⁰. FRC was calculated from the cumulative exhaled He gas volume divided by the differences in end-expiratory He concentrations at the beginning and completion of the washout; values were corrected for mask and apparatus dead space, and converted to BTPS conditions²¹. Results were expressed as the mean value of at least two technically acceptable washouts within 10%. LCI was calculated as the number of FRCs required to decrease the end-expiratory He concentration to 1/40th of the initial value⁵. The LCI results were expressed as the mean value using maneuvers selected to calculate the FRC.

S_{III} was calculated between 60% and 90% of the expired volume from the augmented inflation breaths during the He washout and dead space volume (V_D) was calculated from the first expired breath during the washout using the Fowler technique²² (Figure 3a). Dead space and S_{III} were analyzed only if the expirograms were technically acceptable with a clear phase-I, phase-II and phase-III and expired volumes from at least 2 maneuvers were within 10%. The phase III slope for each washout breath was divided by the mean He gas concentration of each breath (S_N ; ml⁻¹) to adjust for the decreasing He concentration during the washout¹⁶. Figure 3b illustrates that S_{III} decreases and S_N increases with each washout breath. To adjust the normalized slope (S_N) for the effect of somatic size upon expired volume (V_E ; ml) and S_N , a non-dimensional slope (S_{ND}) was calculated by multiplying S_N by V_E ^{16,23}.

Data analysis

Relationships between parameters of ventilation inhomogeneity and age or body length were analyzed using a multi-variate generalized linear model. Mean, standard deviations (SD) and confidence intervals (CI) were used to present continuous variables with normal distribution, while median and inter-quartile range was used for variables with asymmetric distributions. Unpaired t-tests were used to compare means between normally distributed demographic variables, as well as comparing FRC and V_D when expressed in ml/kg. Mann-Whitney test was used for variables with skewed distributions, and Chi-square was employed to compare proportions.

This study has a power to detect the following differences between FT and CLDI: 89% to detect a 4 ml/kg difference in FRC, 92% to detect a 0.8 difference in LCI and 87% to detect a 50 difference in S_{ND} for the first breath.

RESULTS

The washout phase required between 5–7 augmented inflation breaths and was complete within 60 seconds. A total of 65 patients were tested. There were 58 subjects (89%) with technically acceptable and 7 subjects (11%) with technically unacceptable washout curves. In addition, eight patients (12%) did not have two curves with expired volumes within 10% reproducibility. Therefore, data from 15 (23%) subjects was excluded from final analysis.

Fullterm Subjects

The fullterm subjects ($N = 28$) ranged in age from 3 – 28 months and 61% were males. There was a significant correlation between LCI and age ($p = 0.02$), as illustrated in Figure 4; increasing age was associated with decreasing LCI. S_{ND} increased with increasing breath number during the washout ($p < 0.001$), and S_{ND} decreased with increasing age ($p < 0.001$). Figure 5 illustrates S_{ND} versus breath number for subjects grouped as younger than 12 months versus 12 months or older. The younger subject group had significantly higher S_{ND} compared to the older subject group. V_D increased with increasing body length for fullterm subjects ($p < 0.005$). There was no significant relationship between the ratio of dead space volume to the expired volume (V_D/V_E) with age ($p = 0.38$). Neither gender nor race was a significant covariate in any of the analyses. For the fullterm group, coefficient of variation (CV,%) for LCI and S_{ND} were 8.8 and 38.2, respectively and there were no differences in the CV for subjects younger than 12 months and for those older than 12 months.

CLDI Subjects

Demographics for the CLDI subjects and their comparison to fullterm subjects are summarized in Table 1. There were no significant differences between the groups for sex or race, as well as for age or somatic size at the time of evaluation.

There was no significant difference in LCI or FRC between CLDI and FT subjects adjusted for age or body length (Table 2). S_{ND} increased with increasing breath number during the washout; however, there was no difference for the two groups ($p = 0.67$). V_D increased with increasing body length; however, V_D was not significantly different between CLDI and FT subjects. There was also no significant difference in V_D/V_E for CLDI and FT subjects (0.16 ± 0.04 vs. 0.16 ± 0.03 ; $p = 0.62$). Mean expiratory volume during washout was not significantly different for CLDI and FT subjects (27.4 ± 6.9 vs. 26.9 ± 5.0 ml/kg; $p = 0.53$). Coefficient of variation for LCI and S_{ND} were 8.6 and 30.9, respectively.

DISCUSSION

In this study, we described a new methodology for assessing multiple breath inert gas washouts in sedated infants and toddlers. Using augmented inflation breaths to a lung volume above tidal breathing, we were able to obtain inert gas washouts with comparable volumes and rates for all subjects, similar to the approach used in older cooperative subjects who can produce a constant respiratory pattern^{11,12}. The increased inspiratory volume and the slow frequency of the augmented breaths during the washout enabled us to obtain S_{III} during expiration, which generally cannot be measured during normal tidal breathing in this very young age group. Using augmented inflation breaths, we found that ventilation becomes more homogenous with lung growth and maturation early in life. In addition, we found that ventilation inhomogeneity assessed by either LCI or S_{III} was not increased in infants and toddlers with CLDI.

Our study demonstrates that ventilation inhomogeneity within the lung becomes more homogenous with increasing age early in life using two different methods for assessing ventilation inhomogeneity in the lung, LCI and S_{III} . As the normalized slope historically used in adult studies still has the units of liter⁻¹, we used a non-dimensional slope so that we could better evaluate the effect of age, as suggested by other investigators^{16,23}. From the augmented inflation washout breaths, we were also able to calculate V_D , and found that V_D/V_E did not vary with age and suggests that the changes in ventilation inhomogeneity with age were not secondary to changes in the relative contribution of dead space ventilation. We observed a breath by breath increase in S_{ND} during the washout, which is similar to the increase in S_N reported in older cooperative subjects¹¹⁻¹⁶. Our finding that our healthy young subjects had a greater S_{ND} during the washout indicates that these younger healthy subjects had greater ventilation inhomogeneity compared to the older healthy subjects. When the oldest subject (Figure 4) is excluded from the analysis, the relationship remains significant (0.0496).

Our finding that ventilation becomes more homogenous with lung growth early in life is consistent with studies reported for older subjects. Analyzing multiple breath washout by moment analysis, Wall et al reported that ventilation inhomogeneity decreased with increasing age in children between preschool and adolescence⁷. Using slopes of phase III measured from CO₂ expirograms of anesthetized and ventilated subjects, Ream and colleagues reported decreasing slopes with increasing age from infants to adolescents⁶. However, in that analysis, the slopes were not adjusted for the significant increase in expired volume with increasing age. In addition, CO₂ gas exchange can be an important determinant of phase III slope for CO₂. Using an inert gas expired from elevated lung volume, Van Muylem and coworkers reported that S_{III} decreased with increasing somatic size in older children and adolescents⁸. Schulzke and colleagues reported longitudinal data in which LCI decreased in subjects measured as newborns and at 15–18 months of age⁹. Cumulatively, our findings in infants and toddlers, along with published data using other techniques in infants, as well as from older children, strongly suggest that ventilation distribution assessed by inert gas washout improves with lung growth and development. Longitudinal studies from infancy into childhood are required to better define how ventilation inhomogeneity changes with lung growth and development. In addition, use of both He and SF₆ would assist in identifying mechanisms for age related changes.

We did not find that LCI was higher in CLDI subjects using the washout with augmented inflation breaths. This finding suggests that the infants and toddlers with CLDI did not have greater ventilation inhomogeneity compared to full term controls. The absence of a difference in LCI between the CLDI and controls may have resulted from the augmented inflation breaths, which could potentially open airways and make the lung more

homogeneous than would occur during spontaneous tidal breathing. During the execution of a pilot study with multiple augmented inflation breaths, we tried to use smaller sized augmented inflation breaths with an inflation pressures of 10 cm H₂O; however, smaller inflations did not adequately suppress the infant's spontaneous ventilation and washouts were often not successful. Nevertheless, our current results using large augmented inflation breaths are consistent with previous studies that reported no differences in LCI between similar groups of subjects when LCI was measured during tidal breathing. Therefore, we do not think that the augmented inflation breaths minimized differences between CLDI and controls^{9,24,25}. These findings in infants and toddlers with CLDI contrast with the higher values for LCI reported in very young subjects with cystic fibrosis^{1,5} and highlight the different pulmonary pathophysiology of these diseases.

Our LCI values for both groups were higher than values reported for studies of infants assessed by tidal breathing^{9,25}. Our FRC values are similar to previously reported values, which suggest that the slow augmented inflation breaths, which were 3 times larger than tidal breaths, were less efficient than tidal breathing in performing the inert gas washout^{26,27}. Our measured V_D (4.5 ml/kg) from augmented inflation breaths was approximately twice the V_D reported for tidal breathing in this age group²⁸. The larger V_D using the augmented inflation breaths is consistent with the larger airway caliber present at higher lung volumes²⁹; however, the dead space volume to inflation volume is the same or smaller than proportion during tidal breathing so that an increase in dead space ventilation volume does not appear to contribute to lower ventilatory efficiency with the augmented inflation breaths.

We anticipated that phase III slopes would be a more sensitive index than LCI for assessing ventilation inhomogeneity. However, similar to LCI, we did not find a significant difference in S_{ND} between the CLDI and fullterm controls during the washout. Similar results were present using S_N . We also did not find a difference in the size of the augmented breaths delivered to CLDI and fullterm controls, as well as dead space volume, which can potentially increase with ventilation inhomogeneity. Helium is a highly diffusible gas and the diffusion front for He is probably proximal to the acinar region. Therefore, our findings may not detect inhomogeneity within the acinar unit. Use of SF₆ as the inert gas may be more sensitive for detecting intra-acinar differences in ventilation inhomogeneity between CLDI and FT subjects, if these differences are present. Although infants born prematurely with or without CLDI have been reported to have decreased forced expiratory flows, the cumulative findings from our study, as well as from other investigators, strongly suggest that ventilation inhomogeneity is not a significant component of the airway pathophysiology of infants and toddlers with CLDI^{9,24,25}.

In summary, we describe a new methodology for obtaining MBWO with augmented breaths, which enables the assessment of LCI, S_{ND} , V_D , and FRC. We found that with lung growth and maturation early in life, ventilation becomes more homogenous. Using this new technique, we also found no evidence that ventilation inhomogeneity is a significant component of the pulmonary pathophysiology of CLDI.

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5.

Table 1

Demographics for fullterm Control and CLDI subjects

	Full Term	CLDI	p value
Number of subjects	28	22	
Gestational age at birth (weeks)	39.0 (0.8)	26.0 (1.8)	< 0.001
Birth weight (kg)	3.3 (0.4)	1.0 (0.2)	< 0.001
Sex (% male)	61	41	0.16
Race (% Caucasian)	65	68	0.77
Days of mechanical ventilation ^a	-	14.0 (2 to 43) <i>b</i>	
Days of supplemental oxygen	-	78 (59 to 102) <i>b</i>	
Corrected-age at testing (months)	11.9 (5.9)	12.2 (3.3)	0.82
Length at testing (cm)	72.6 (7.7)	72.7 (4.9)	0.96
Length (z-score)	-0.69 (-1.25 to 0.06)	-1.25 (-1.58 to 0.19) <i>b</i>	0.11
Weight at Testing (kg)	9.2 (2.0)	9.2 (1.6)	0.93
Weight (z-score)	-0.07 (-0.61 to 0.59)	-0.29 (-1.12 to 0.43) <i>b</i>	0.61

Results expressed as means (SD), unless indicated by *b* for median (inter-quartile range).^a CPAP not included.

Table 2Comparison of full-term control and CLDI subjects (LCI, FRC, S_{ND} , V_D).

	Full Term	CLDI	p value
LCI	9.3 (9.1 – 9.6)	9.5 (9.2 – 9.8)	0.56
FRC (ml)	183 (169 – 197)	172 (157 – 188)	0.32
FRC (ml/kg)	19.9 (18.3 – 21.5)	18.7 (17.0 – 20.4)	0.33
S_{ND}	211 (198 – 225)	218 (202 – 233)	0.55
V_D (ml)	40.9 (36.3 – 45.6)	42.1 (36.8 – 47.4)	0.75
V_D (ml/kg)	4.4 (3.9 – 4.9)	4.6 (4.0 – 5.2)	0.57

Results expressed as means (95% confidence interval). LCI = lung clearance index adjusted for age. FRC = functional residual capacity adjusted for body length; S_{ND} = non-dimensional phase III slope adjusted for age and breath number; V_D = dead space adjusted for body length and calculated from first breath.