Membrane and Capillary Components of Lung Diffusion in Infants with Bronchopulmonary Dysplasia

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Abstract

Rationale: Autopsied lungs of infants with bronchopulmonary dysplasia (BPD) demonstrate impaired alveolar development with larger and fewer alveoli, which is consistent with our previous physiologic findings of lower pulmonary diffusing capacity of the lung for carbon monoxide (DL_{CO}) in infants and toddlers with BPD compared with healthy controls born at full term (FT). However, it is not known whether the decreased DL_{CO} in infants with BPD results from a reduction in both components of DL_{CO} : pulmonary membrane diffusing capacity (DM) and V_c .

Objectives: We hypothesized that impairment of alveolar development in BPD results in a decrease in both DM and V_c components of DL_{CO} but that the DM/V_c ratio would not differ between the BPD and FT groups.

Methods: DL_{CO} was measured under conditions of room air and high inspired oxygen (90%), which enabled DM and V_c to be calculated.

Measurements and Main Results: DM and V_c increased with increasing body length; however, infants with BPD had significantly lower DM and V_c than FT subjects after adjustment for race, sex, body length, and corrected age. In contrast to DM and V_c , the DM/V_c ratio remained constant with increasing body length and did not differ for infants with BPD and FT subjects.

Conclusions: Our findings are consistent with infants with BPD having impaired alveolar development with fewer but larger alveoli, as well as a reduced V_c .

Keywords: bronchopulmonary dysplasia; infants; lung growth; pulmonary diffusion capacity

At a Glance Commentary

Scientific Knowledge on the Subject: In previous studies in animal models, researchers determined that bronchopulmonary dysplasia (BPD) results in impaired alveolar development with fewer and larger alveoli; however, the alveolar–capillary unit had an alveolar surface area similar to capillary vessels in BPD and control animals.

What This Study Adds to the Field: We demonstrate that the reduced diffusing capacity of carbon monoxide in infants with BPD is secondary to comparable reductions in pulmonary membrane diffusing capacity and pulmonary capillary blood volume. These new *in vivo* physiologic findings in infants with BPD are consistent with pathologic reports of impaired alveolar development with not only fewer but also larger alveoli, which reduces alveolar surface area as well as pulmonary capillary density.

During the past decades, infants born extremely prematurely have survived because of advances in neonatal care and use of maternal corticosteroids and exogenous

surfactants; however, the incidence of bronchopulmonary dysplasia (BPD) remains high (1–3). Autopsied lungs from infants with BPD demonstrate impaired

alveolar development with larger and fewer alveoli and decreased pulmonary capillary density (4–7). These pathologic findings are consistent with our previous findings that

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infants with BPD had lower pulmonary diffusing capacity of the lung for carbon monoxide (DL_{CO}), but similar V_A , compared with healthy full-term (FT) infants (8). We recently demonstrated in a murine model that there is an overall decrement of alveolar surface area and pulmonary vessels in BPD; however, when pulmonary vessels are expressed as vessels relative to septal tissue, there is no difference between BPD and control animals (9). This latter finding suggests that the impaired alveolar development results from fewer and larger alveoli; however, the alveolar-capillary unit has an alveolar surface area similar to capillary vessels of BPD and control animals. DL_{CO} is determined by the pulmonary membrane diffusing capacity (DM) and the V_c , which can be calculated by measuring DL_{CO} under conditions of room air and high inspired oxygen, as initially described by Roughton and Forster (10). Under hyperoxic conditions, the increased alveolar oxygen tension increases oxygen binding to Hb and reduces carbon monoxide uptake, which decreases DL_{CO} values under high inspired oxygen concentrations compared with room air (11). DL_{CO} measurements under these two different conditions of alveolar oxygen concentration enables the calculation of DM and V_c , which provides a physiologic estimate of these two components of lung diffusion and thus reveals the underlying pathophysiology of BPD.

The purpose of our study was to assess DM and V_c in infants and toddlers with BPD. We hypothesized that if BPD is associated with impaired alveolar development, infants with BPD would have lower DM and V_c ; however, the ratio (DM/V_c) would not differ from that of healthy controls. Some of the results of this study were reported previously in the form of an abstract (12).

Methods

Subjects

Preterm infants with BPD. Subjects born at between 23 and 30 weeks of gestation and having a diagnosis of BPD were recruited from the Neonatal Intensive Care Unit or the Pediatric Pulmonary Clinic of James Whitcomb Riley Hospital for Children (Indianapolis, IN) between 2008 and 2012.

Table 1. Subject Demographics

Characteristic	FT	BPD	P Value*
Subjects, n	34	51	
Gestational age, wk	39.4 (0.9)	26.1 (1.7)	<0.001
Female sex, n (%)	19 (56)	28 (55)	0.93
White race, n (%)	21 (62)	37 (72)	0.30
Age corrected, mo	15.9 (9.3)	17.4 (5.2)	0.40
Body length, cm	76.4 (9.4)	75 (6.5)	0.43
Hb, g/dl	12.1 (1.2)	12.6 (1.1)	0.033

Definition of abbreviations: BPD = subjects with bronchopulmonary dysplasia; FT = healthy full-term. Values are means (SD) for all variables except sex and race, which are represented by frequency and percent for the given categories.

*Two-sample *t* tests were used for continuous variables, and χ^2 tests were used for categorical variables.

BPD was defined as an oxygen requirement ($>21\% F_{IO_2}$) for at least 28 days. Subjects were clinically stable outpatients with no oxygen requirement at the time of testing and no acute respiratory symptoms for at least 3 weeks.

Healthy full-term infants. Subjects born at 37 weeks of gestation or later were recruited through advertisements in local publications in Indianapolis, Indiana, between 2008 and 2013. All subjects had no cardiorespiratory malformations, and all had a respiratory history negative for wheezing, asthma, treatment with asthma medications, or hospitalization for a respiratory illness.

Subjects were evaluated between 2008 and 2013 at James Whitcomb Riley Hospital for Children while sleeping in a supine position with chloral hydrate sedation (50–100 mg/kg). Oxygen saturation and heart rate were monitored during testing as recommended in American Thoracic Society/European Respiratory Society guidelines (13). The study was approved by the institutional review board at Indiana University, and parental informed consent was obtained. DL_{CO} values measured on

room air were previously reported for 18 subjects with BPD and 25 FT infants (8, 14).

Measurements and Calculations

DL_{CO} and V_A were measured using normoxic (20% oxygen, 4% helium, and 0.3% CO^{18}) and hyperoxic (90% oxygen, 4% helium, and 0.3% CO^{18}) test gases and a 4-second induced respiratory pause at an inflation airway pressure of 30 cm H_2O , as previously described (8, 14, 15). For each test gas, DL_{CO} was expressed as the average of two or three measurements within 10% and adjusted for Hb concentration, as recommended by the American Thoracic Society/European Respiratory Society Task Force (16). DM and V_c were calculated as described by Roughton and Forster (10, 14).

Statistical Analysis

Descriptive statistics included mean and range for continuous variables. Demographic and lung function data for each group (BPD and FT) were compared using two-sample *t* tests for continuous variables and χ^2 tests for categorical

Table 2. Pulmonary Diffusion Capacity and Alveolar Volume

	FT	BPD	P Value*
DL_{CO} -RA STPD, ml/min/mm Hg	4.0 (1.3)	3.3 (1.0)	0.017
DL_{CO} -High O_2 STPD, ml/min/mm Hg	2.0 (0.7)	1.7 (0.5)	0.036
V_A , ml	611.1 (229.7)	586.6 (185.4)	0.59

Definition of abbreviations: BPD = bronchopulmonary dysplasia; DL_{CO} -High = pulmonary diffusion capacity of the lung for carbon monoxide measured with hyperoxic test gas; DL_{CO} -RA = pulmonary diffusion capacity of the lung for carbon monoxide measured with normoxic test gas; FT = healthy full-term; STPD = standard temperature and pressure, dry.

Values are means (SD) for all variables.

*Two-sample *t* test.

variables. If the continuous variables had nonnormal distributions, the Wilcoxon nonparametric test was used. Linear regression models were used to evaluate relationships between D_{LCO} , D_M , V_c , and body length. Analysis of covariance was performed to determine a group effect on lung diffusion variables adjusted for sex, race, and corrected age and body length at testing. For all analyses, the level for statistical significance was set at 0.05. Statistical analysis was performed with IBM SPSS Statistics 22 software (IBM, Armonk, NY).

Results

Subjects

We evaluated 85 infants and toddlers with corrected ages between 3 and 37 months. The demographics of the subjects with BPD and the FT infants are summarized in Table 1. The subjects with BPD were born prematurely and therefore had younger gestational ages at birth than the FT infants. There were no significant differences between BPD and FT groups with regard to sex, race, and corrected age and body length at the time of testing.

D_{LCO} and V_A

Group mean values for pulmonary diffusion are summarized in Table 2. Subjects with BPD had significantly lower D_{LCO} compared with FT infants when measured while breathing the normoxic and the hyperoxic gas mixtures. V_A was not significantly different between subjects with BPD and FT infants.

D_M , V_c , and D_M/V_c

D_M and V_c increased with increasing body length in the subjects with BPD and the FT infants, as illustrated in Figures 1A and 1B. Subjects with BPD had significantly lower D_M and V_c than FT subjects after adjustment for body length. In contrast to D_M and V_c , the D_M/V_c ratio remained constant with increasing body length for the infants with BPD and the FT subjects, and there was no difference in D_M/V_c ratio for the two groups (Figure 1C).

Table 3 summarizes the comparisons of D_M and V_c for BPD and FT subjects, adjusted for race, sex, corrected age, and body length. Subjects with BPD had lower D_M and V_c than FT infants. Among the

Figure 1. Relationships between components of pulmonary diffusion capacity and body length. (A) Pulmonary membrane diffusing capacity (D_M) versus body length in subjects with bronchopulmonary dysplasia (BPD) (circles; $n = 51$) and healthy full-term (FT) infants (triangles; $n = 34$). There was a significant relationship between D_M and body length in subjects with BPD ($R^2 = 0.58$, $P < 0.0001$) as well as in FT infants ($R^2 = 0.74$, $P < 0.0001$). Compared with FT infants, subjects with BPD had significantly lower D_M ($P = 0.0023$) after adjustment for body length. (B) V_c versus body length in subjects with BPD (circles; $n = 51$) and FT infants (triangles; $n = 34$). There was a significant relationship between V_c and body length in subjects with BPD ($R^2 = 0.60$, $P < 0.0001$) and FT infants ($R^2 = 0.71$, $P < 0.0001$). Compared with FT infants, subjects with BPD had significantly lower V_c after adjustment for body length ($P = 0.023$). (C) D_M/V_c ratio versus body length in subjects with BPD (circles; $n = 51$) and FT infants (triangles; $n = 34$). There was no relationship between D_M/V_c ratio and body length in subjects with BPD and FT infants ($P = 0.43$ and $P = 0.76$, respectively). There was no difference in D_M/V_c ratio between subjects with BPD and FT infants (0.61 vs. 0.65, respectively; $P = 0.60$). STPD = standard temperature and pressure, dry.

Table 3. Components of Pulmonary Diffusing Capacity

Variable	D _M				V _c			
	Estimate	SE	95% CI	P Value*	Estimate	SE	95% CI	P Value*
FT	Reference				Reference			
BPD	−0.963	0.306	0.355–1.571	0.002	−1.665	0.465	0.739–2.591	0.001
Race (W = 1, NW = 2)	−0.930	0.296	−1.519 to −0.340	0.002	−0.933	0.451	−1.831 to −0.036	0.042
Sex (M = 1, F = 0)	0.332	0.277	−0.220 to 0.884	0.235	0.756	0.422	−0.084 to 1.596	0.077
Body length, cm	0.244	0.042	0.162–0.327	0.000	0.181	0.063	0.055–0.307	0.005
Age _{CORR} , mo	−0.025	0.045	−0.115 to 0.065	0.582	0.193	0.069	0.056–0.330	0.006
Intercept	−11.052	2.51	−16.041 to −6.062	0.000	−6.496	3.82	−14.095 to 1.104	0.093

Definition of abbreviations: Age_{CORR} = corrected age; BPD = bronchopulmonary dysplasia; CI = confidence interval; D_M = pulmonary membrane diffusion capacity; FT = healthy full term; NW = nonwhite; W = white.

*Analysis of covariance.

covariates analyzed, D_M and V_c increased with increasing body length, and whites had higher D_M and V_c than nonwhites; however, sex did not reach statistical significance. Increasing corrected age at time of testing was associated with increasing V_c but not D_M. Subjects with BPD compared with FT subjects did not differ for D_M/V_c ratio (0.61 vs. 0.65, respectively; *P* = 0.60).

Discussion

To our knowledge, the present study is the first to demonstrate that the reduced D_{LCO} in infants with BPD is secondary to comparable reductions in D_M and V_c. These new *in vivo* physiologic findings in infants with BPD are consistent with pathologic reports of impaired alveolar development with not only fewer but also larger alveoli, which reduces alveolar surface area as well as pulmonary capillary density.

In the present study, we found that D_M and V_c increased with increasing somatic size, which is consistent with morphometric studies indicating that alveolarization increases alveolar membrane surface area and pulmonary capillaries with growth (17, 18). We also found that after adjusting for somatic size as well as other potential confounders (sex, race, and corrected age), infants with BPD had significantly lower values for both D_M and V_c than FT infants, which is consistent with reductions in alveolar surface area and V_c as reported on the basis of pathologic specimens (4, 5, 19–21). Although the BPD lung has less alveolar surface area and fewer pulmonary capillary vessels, the similar D_M/V_c ratios for subjects with BPD and FT infants is most consistent with the larger but fewer

alveolar–capillary units developing with alveolar surface area matched to V_c for gas exchange.

We were not able to obtain physiologic and morphometric measurements from infants with BPD; however, animal models can provide some additional insight into this relationship. The hyperoxia neonatal murine model of BPD exhibits impaired alveolar development with fewer but larger alveoli and fewer pulmonary vessels per high-powered field (22–24), which reflects less parenchymal tissue relative to lung volume. We recently demonstrated that when pulmonary vessels are expressed as vessels relative to septal tissue rather than as vessels per high-powered field, there is no difference between BPD and control animals (9). This morphometric finding is similar to the present physiologic findings of no difference between infants with BPD and FT subjects for D_M/V_c, and it suggests that the alveolar–capillary unit in BPD has similar alveolar surface area relative to capillary vessels but less surface area and fewer vessels secondary to lack of septation. In our murine studies, we also found significant correlations between physiologic measurements of pulmonary diffusion and morphometric measurements of lung parenchymal structure, which support our findings in infants with BPD that decreased D_M and V_c, but normal D_M/V_c, result from impaired alveolar development, with fewer and larger alveoli and a comparable decrease in pulmonary capillaries.

Researchers in studies of children and adults with a prior history of BPD have reported lower D_{LCO} (25–27) than healthy controls; however, we are not aware of any previous study evaluating the D_M and V_c in subjects with a history of BPD. Studies in adults with differing pulmonary diseases,

including chronic obstructive pulmonary disease (28), pulmonary hypertension (29), and idiopathic interstitial pneumonia (30), have demonstrated reductions in both D_M and V_c. However, D_M/V_c ratios were increased in chronic obstructive pulmonary disease, reduced in pulmonary hypertension, and unchanged in idiopathic interstitial pneumonia, which may reflect the differing pathophysiology of these diseases. Although the clinical relevance of our findings are unclear, the possibility of measuring D_M and V_c in infants with BPD may allow the future assessment of therapies targeted at impaired alveolar development, which includes both the membrane and vascular components of the alveolar–capillary unit.

Our study has several limitations. BPD classification was based on the clinical decision to use supplemental oxygen rather than a physiologic room air challenge. Therefore, some of our premature infants may have had less severe lung disease, and we would thus have underestimated the difference between BPD and FT infants. We assessed D_M and V_c using the classic technique of measuring D_{LCO} under conditions of room air and high oxygen. Infants with BPD may exhibit pulmonary vasodilation with hyperoxia, which could alter V_c. However, our infants with BPD did not have a diagnosis of pulmonary hypertension and did not require supplemental oxygen at the time of evaluation. In addition, subjects with BPD and FT infants exhibited similar differences in D_{LCO} when measured while breathing room air and high oxygen, which suggests the absence of vasodilation in the infants with BPD. Limiting our study to infants with BPD who were clinically stable outpatients without an oxygen requirement

at the time of evaluation does not enable us to extrapolate our findings to subjects with more severe respiratory disease. However, our physiologic findings demonstrate that infants with less severe BPD still have impaired alveolar development. In future studies, investigators could evaluate subjects with more severe pulmonary disease and a persistent oxygen requirement by using 40% and 90% FiO_2 . Last, our data are

cross-sectional; a longitudinal evaluation is required to evaluate lung growth and to determine whether infants with BPD exhibit catchup in alveolar development or have a persistent deficit.

In summary, we partitioned pulmonary diffusion capacity into its DM and Vc components in infants with BPD. We found that DM and Vc were comparably decreased in subjects with BPD and FT infants, which is most consistent with

impaired alveolar development in the infants with BPD. Measurements of pulmonary diffusion and its components may be an important physiologic outcome to characterize in assessing the effects of premature birth and therapeutic strategies designed to minimize the development of BPD or to stimulate alveolar growth. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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