ORIGINAL ARTICLE

Magnetic Resonance Imaging Evaluation of Regional Lung V_Ts in Severe Neonatal Bronchopulmonary Dysplasia

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Abstract

Rationale: Bronchopulmonary dysplasia is a heterogeneous lung disease characterized by regions of cysts and fibrosis, but methods for evaluating lung function are limited to whole lung rather than specific regions of interest.

Objectives: Respiratory-gated, ultrashort echo time magnetic resonance imaging was used to test the hypothesis that cystic regions of the lung will exhibit a quantifiable V_T that will correlate with ventilator settings and clinical outcomes.

Methods: Magnetic resonance images of 17 nonsedated, quiet-breathing infants with severe bronchopulmonary dysplasia were reconstructed into end-inspiration and end-expiration images. Cysts were identified and measured by using density threshold combined with manual identification and segmentation. Regional V_Ts were calculated by subtracting end-expiration from end-inspiration volumes in total lung, noncystic lung, total-cystic lung, and individual large cysts.

Measurements and Main Results: Cystic lung areas averaged larger V_Ts than noncystic lung when normalized by volume (0.8 ml V_T/ml lung vs. 0.1 ml V_T/ml lung, $P < 0.002$). Cyst V_T correlates with cyst size ($P = 0.012$ for total lung cyst and $P < 0.002$ for large cysts), although there was variability between individual cyst V_T, with 22% of cysts demonstrating negative V_T. Peak inspiratory pressure positively correlated with total lung V_T ($P = 0.027$) and noncystic V_T ($P = 0.015$) but not total lung cyst V_T ($P = 0.8$). Inspiratory time and respiratory rate did not improve V_T of any analyzed lung region.

Conclusions: Cystic lung has greater normalized V_T when compared with noncystic lung. Ventilator pressure increases noncystic lung V_T, but inspiratory time does not correlate with V_T of normal or cystic lung.

Keywords: neonatal; respiratory physiology; tidal volume; ultrashort echo time; premature

One of the most common morbidities in premature infants is chronic lung disease of prematurity or bronchopulmonary dysplasia (BPD) (1–3). The diagnosis of BPD has steadily increased since its initial recognition, largely because improvements in neonatal care have increased survival rates in the smallest infants who more commonly develop BPD (4). Although the

precise pathogenesis of BPD is poorly understood (5), BPD parenchymal lung disease is anatomically categorized by heterogeneous areas of simplified alveoli (cysts), fibrosis, and emphysema (1, 2, 6).

As the incidence of BPD increases, it is critical to optimize treatment for this delicate and growing population. Most research has targeted early-phase treatment

and prevention (7), but some of the most difficult patients to manage are the patients with later-phase severe BPD (sBPD) (2, 8, 9). There is limited evidence supporting management strategies for infants with established BPD, especially regarding mechanical ventilation. Current theory of ventilation for BPD is divided into early and late phase. Early-phase ventilation is

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At a Glance Commentary

Scientific Knowledge on the

Subject: Bronchopulmonary dysplasia is one of the most common morbidities in premature infants and is anatomically categorized by heterogeneous areas of simplified alveoli (cysts), fibrosis, and emphysema. Our understanding of the heterogeneous nature of severe bronchopulmonary dysplasia lung disease has been limited by the lack of objective analysis of the regional lung structure and respiratory mechanics.

What This Study Adds to the Field:

We used ultrashort echo time magnetic resonance imaging to evaluate air movement through cystic and noncystic regions of the lung. We found that cystic regions of the lung are not merely trapped air and that cystic lung has greater normalized V_T when compared with noncystic lung. Ventilator pressure increases noncystic lung V_T , but inspiratory time and respiratory rates do not correlate with V_T of normal or cystic lung.

aimed at prevention of BPD and designed for a relatively uniform lung. Based on current theory, optimal early-phase ventilator strategy is a fast-respiratory rate, low V_T , and short inspiratory time (T_i). For sBPD, as the lung progresses into the late phase of the disease, there is varying airway resistance, lung compliance, and time constants. It is believed that optimal ventilation of late-phase sBPD lungs is a slow respiratory rate, a large V_T , and a long T_i (10, 11). Although widely accepted, there is limited evidence to support this late-phase approach, partly because most methods for analyzing lung function are difficult to carry out in infants and limited to whole lung measurements rather than evaluation of the individual regions of the heterogeneous sBPD lung.

Ultrashort echo time (UTE) magnetic resonance imaging (MRI) can obtain high-resolution images of the lung in quiet-breathing, nonsedated infants (12–16). Because UTE images capture the entire lung over a period of time, bulk motion artifact can be retroactively removed, and

data can be grouped into images of end inspiration and end expiration (12). Lung V_T s can be determined by subtracting end-expiration lung volume from end-inspiration lung volume (17). This approach can be used to objectively determine V_T s of individual regions of the heterogeneous BPD lung, including areas of alveolar simplification, cysts, and emphysema.

We hypothesized that areas of cystic dysplasia seen in the lung parenchyma of infants with sBPD will exhibit a quantifiable V_T , and the V_T will be affected by ventilator parameters such as peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), and T_i . To test this, we used UTE MRI to measure total lung V_T , noncystic lung V_T , total lung cyst V_T , and individual large cyst V_T and compared these measurements to clinical outcomes and ventilator variables.

Methods

Study Patients

Premature infants with BPD were recruited from the neonatal ICU (NICU) at Cincinnati Children's Hospital Medical Center with Institutional Review Board approval and informed parental consent. Infants in the BPD group were eligible for participation if they had history of prematurity (defined as gestational age at time of delivery of less than 37 wk), had BPD (based on the current National Institute of Child Health and Human Development and the NHLBI consensus definitions), and received a chest MRI as part of a larger study from June 2017 to December 2018. BPD severity was further

defined based on the criteria described by Jensen and colleagues (18). Clinical variables that vary continuously (e.g., oxygen saturations, F_{iO_2} , respiratory rate, and CO_2 [determined by capillary blood gas] levels) were collected surrounding the time of the MRI. All other clinical variables were gathered on the day of the MRI.

Exclusion criteria were defined as suspected muscular dystrophy, suspected neurologic disorder, or significant genetic or chromosomal abnormalities that may affect lung development; evidence of any respiratory infection at time of imaging; and normal MRI exclusionary criteria. Patients were also excluded if the MRI had significant bulk motion artifact.

A control group of infants who were delivered at 36–37 weeks' gestation, did not have BPD or meet any of the exclusion criteria stated above, and received a chest MRI as part of the same study from June 2017 to December 2018 were used.

MRI Acquisition and Reconstruction

All imaging was performed by using a unique neonatal-sized 1.5T scanner located in the NICU at Cincinnati Children's Hospital Medical Center (originally ONI Medical Systems; currently GE Healthcare) (19, 20). High-resolution proton density-weighted images of pulmonary structures were acquired in each subject by using a neonatal-specific three-dimensional radial UTE pulse sequence (19, 21–23). Typical UTE acquisition parameters were as follows: repetition time and echo time = 5 and 0.2 ms; flip angle = 5°; bandwidth = ± 125 kHz; field of view = 18 cm; three-dimensional isotropic resolution = 0.7 mm (identical resolution in

Figure 1. Example of three-dimensional thresholding segmentations of cystic areas at end expiration and end inspiration from ultrashort echo time magnetic resonance imaging.

Table 1. Characteristics of the Study Cohort and Control Patients

Patient	PMA at Birth (wk)	Birth Weight (kg)	Sex (M or F)	PMA at MRI (wk)	MRI Weight (kg)	BPD Grade*	Bronchodilator	PH Therapy	Interface	Ventilator Mode
BPD 1	26.4	1	M	39.0	3.50	3	N	N	ETT	PC SIMV + PS
BPD 2	27.9	0.58	M	49.3	3.80	3	N	Y	Trach	PC SIMV + PS
BPD 3	27.3	0.75	F	44.6	3.52	3	N	N	ETT	PC SIMV + PS
BPD 4	24.4	0.7	F	39.7	3.50	3	N	N	ETT	PC SIMV + PS
BPD 5	24.0	0.48	F	41.4	3.01	3	N	Y	ETT	PC SIMV + PS
BPD 6	29.6	0.96	M	43.6	3.50	2	N	N	Nasal cannula	NIPPV
BPD 7	24.7	0.52	F	40.7	2.96	3	N	N	ETT	PC SIMV + PS
BPD 8	25.1	0.61	F	41.6	3.09	No	N	N	Room air	Room air
BPD 9	25.6	0.78	F	42.6	3.07	3	N	N	Nasal cannula	CPAP
BPD 10	26.7	0.54	F	42.1	2.50	3	N	N	ETT	APRV
BPD 11	29.6	1.72	M	39.0	3.80	3	N	Y	ETT	PRVC SIMV + PS
BPD 12	25.7	0.54	M	45.1	4.09	3	N	Y	Nasal mask	CPAP
BPD 13	24.4	0.8	M	41.1	3.20	3	N	N	ETT	PRVC SIMV + PS
BPD 14	28.0	0.75	F	44.9	4.20	3	N	N	ETT	PRVC SIMV + PS
BPD 15	25.6	0.62	F	39.9	2.10	3	N	N	ETT	PRVC SIMV + PS
BPD 16	25.4	0.79	F	38.4	2.49	3	N	N	ETT	PRVC SIMV + PS
BPD 17	26.0	0.98	M	39.6	4.20	3	N	N	ETT	PRVC SIMV + PS
Control	36.1	2.575	F	41.0	3.61	2	—	—	Nasal cannula	PC SIMV + PS
Control	36.0	2.71	M	40.3	3.90	Gastroschisis MMC	—	—	Room air	Room air
Control	37.1	2.78	F	39.6	2.85	Ovarian mass	—	—	Room air	Room air

Definition of abbreviations: APRV = airway pressure release ventilation; BPD = bronchopulmonary dysplasia; CPAP = continuous positive airway pressure; ETT = endotracheal tube; MMC = myelomeningocele; MRI = magnetic resonance imaging; N = no; NIPPV = noninvasive positive pressure ventilation; PC SIMV + PS = pressure control synchronized intermittent mandatory ventilation + pressure support; PH = pulmonary hypertension; PMA = postmenstrual age; PRVC SIMV + PS = pressure-regulated volume control synchronized intermittent mandatory ventilation + pressure support; Trach = tracheostomy; Y = yes.

*Based on the grading system defined by Jensen and colleagues, 2019 (18).

Figure 2. Correlations of V_T to (A) total lung cyst volume at end expiration ($P=0.012$) and (B) large cyst volume at end expiration ($P<0.002$). Plot elements are as follows: expiration volume of infants with bronchopulmonary dysplasia (solid circle) and expiration volume of control patients (open square). TV = tidal volume.

all directions); scan time ~ 16 minutes; and number of radial projections = 200,000.

Respiratory-gated images were reconstructed at end expiration and end inspiration by using previously published methods that retrospectively exploit the motion-modulation of the center of k-space in radial acquisitions (12, 24). Images were grouped at the top and bottom 25% of the respiratory cycle, and then reconstructed after discarding data acquired during bulk motion intervals, using a motion-tracking technique for radial k-space trajectories similar to that used for respiratory gating (14). This technique provides sufficient data to produce detailed images of the lung while continuing to allow images to be separated into individual parts of the respiratory cycle.

Image Analysis

Whole lung volume. Images were generated semiautomatically from end-inspiration and end-expiration images for each study participant through Amira (FEI Visualization Sciences Group) and included all lung tissue, vasculature, and airways.

Large cyst volume. In the 16 patients with cysts that were large enough to be clearly visible, individual cysts were segmented at end expiration and end inspiration. The average reader-to-reader variability in determining cyst size was found to be 0.00043 ± 0.00067 ml on cysts ranging from 0.0129 to 0.213 ml in size. All visible cysts were segmented up to a maximum of nine cysts per infant. In the six infants in whom the lung parenchyma

possessed more than nine visible cysts, a randomized sampling was taken to include three small, three medium, and three large cysts from varying regions. Readers were blinded to the clinical status or respiratory parameters of the patient during the large cyst segmentation process.

Total lung cyst volume. Because of limited image resolution compared with cyst size, the evaluation of smaller cysts was not possible with the individual cyst segmentation method used above; therefore, a total lung evaluation based on cyst density was used (Figure 1). Because UTE MRI was acquired in the proton density regime, it can be used to obtain computed tomography-like quantification of the lung density in grams per cubic centimeter after normalization to a smooth muscle density standard (16). A UTE MRI voxel is a $0.7 \times 0.7 \times 0.7$ mm (or 0.347 microliter) cube of lung, which should contain 520 alveoli based on normal alveoli size (25). Parenchymal cysts are made up of simplified alveoli, making them less dense than healthy lung parenchyma. To find the upper limit of the voxel density of a cyst, 18 large cysts were randomly selected throughout the lung from three patients and segmented at end inspiration and at end expiration, and the average density of each cyst was determined. A lung cyst the size of at least 520 alveoli could then be defined as any voxel or collection of voxels within the lung with an area of density less than or equal to the density of a large cyst. This density-based definition of total lung cyst will therefore include all small cysts, large cysts, bullae, airways, and low

Figure 3. Correlations of percentage of cystic lung volume per total lung volume to (A) patient CO_2 level ($P=0.96$), (B) patient oxygen saturation/ FiO_2 ($P=0.09$), and (C) patient respiratory severity index ($P=0.47$). Resp = respiratory.

Figure 4. Correlations of CO_2 to (A) total lung $\dot{V}_E$ (solid circles; $P=0.52$) and total lung cyst $\dot{V}_E$ (open triangles; $P=0.24$) and (B) large cyst (solid circles; $P=0.93$).

signal noise within the region of lung analyzed.

Noncystic lung volume. The noncystic lung volume was calculated by subtracting the total lung cysts volume from the total lung volume. The remaining volume included the volume of the normal and hyperdense regions of the lung. The hyperdense measurements represent regions of atelectasis, fibrotic tissue, and high signal intensity noise.

Statistical Analysis

Results were evaluated using Student's *t* test. Cyst data was not normally distributed and was compared with Spearman rank correlation test. The corresponding *P* value was used to determine statistical significance at a significance level of 0.05.

Results

The study cohort was composed of 17 infants with sBPD and 3 control infants from the Cincinnati Children's Hospital Medical Center NICU (Table 1). The mean birth weight was 0.94 ± 0.81 kg in the infants with BPD and 2.69 ± 0.10 kg in the control infants. The mean gestational age at birth was 26.1 ± 1.7 weeks for the infants with BPD and 36.3 ± 0.5 weeks in the control infants. The mean postmenstrual age at the time of the MRI was 41.7 ± 2.8 weeks in the infants with BPD and 40.3 ± 0.70 weeks in the control infants. The mean weight at the time of the MRI was 3.3 ± 0.5 kg in the infants with BPD and 3.5 ± 0.5 kg in the control infants.

To determine if cysts are capable of a measurable V_T and if this V_T correlates with cyst size, total lung cyst and large cyst expiration volume were compared with their V_T s. There was a significant correlation between total lung cysts expiration volume and V_T ($r=0.59$; $P<0.012$) (Figure 2A) and between large cyst expiration volume and V_T ($r=0.41$; $P<0.002$) (Figure 2B). When V_T was normalized to the volume of the corresponding lung region (e.g., $V_T/\text{expiratory volume}$), the average total lung cyst V_T was greater than the noncystic V_T (0.8 vs. 0.1 ; $P<0.002$). Because the density-based definition of total lung cysts also includes lung volume occupied by airways, and movement within this airway space can contribute to the total lung cyst V_T , the total lung cyst V_T was also determined in a non-BPD control group that had comparable airway movement without additional cystic lung disease. There was minimal total lung cyst V_T in the control group, suggesting that the majority of the total lung cyst V_T observed in the BPD population was because of cystic V_T and that airway movement did not significantly contribute to total lung cyst V_T (Figure 2A, open squares). The results above revealed a significant positive correlation between the volume of cysts and the measured cysts V_T ; however, we did observe a marked variability in the large cyst V_T , with 22% of the large cysts demonstrating negative V_T s.

The percentage of total lung cyst volume to total lung volume was compared with CO_2 (Figure 3A), oxygen saturation/ FiO_2 (Figure 3B), and the

respiratory severity index (mean airway pressure $\times \text{FiO}_2$) (Figure 3C), all measured on the same day as the MRI. There was a trend toward worsening oxygenation (as defined by oxygen saturation/ FiO_2 ; $P=0.09$) with increasing percentage of lung volume occupied by cysts, but there was no correlation between the percentage of lung volume occupied by cysts and clinical disease severity when determined by patient CO_2 levels ($P=0.96$) or respiratory severity index ($P=0.47$).

MRI-based total lung and regional V_T s were paired with patient respiratory rates averaged during the time of their MRI to determine $\dot{V}_E$, and these values were compared with patient CO_2 levels at the time of MRI to determine if cyst air movement contributed to CO_2 removal. Total lung $\dot{V}_E$ did not significantly correlate ($P=0.52$) with CO_2 (Figure 4). In addition, total lung cysts and large cyst $\dot{V}_E$ did not significantly correlate with CO_2 ($P=0.24$ and $P=0.93$, respectively). However, total lung and total lung cyst $\dot{V}_E$ versus CO_2 had nearly identical slopes (slope = -0.019 and slope = -0.017 , respectively).

To determine ventilator effects on air movement, ventilation parameters averaged from the day of the MRI were compared with V_T of the total lung, total lung cysts, large cyst, and noncystic regions. There was a significant positive correlation between PIP and lung V_T ($P=0.027$) (Figure 5A) and noncystic region V_T ($P=0.016$) (Figure 5A). However, total lung cysts V_T ($P=0.80$) (Figure 5A) and large cyst V_T ($P=0.97$) (Figure 5E) did not correlate significantly with PIP.

Lung V_T and total lung cyst V_T did not reach statistical significance ($P=0.24$ and 0.81 , respectively) when compared with PEEP, but both demonstrated a positive trend (Figure 5B). Both large cyst V_T and noncystic lung V_T did not significantly correlate with PEEP ($P=0.19$ and $P=0.39$, respectively) (Figures 5B and 5F).

Lung V_T , total lung cyst V_T , and large cyst V_T did not significantly correlate with Ti ($P=0.57$, $P=0.22$, and $P=0.48$, respectively) (Figures 5C and 5G) or ventilator respiratory rate ($P=0.86$, $P=0.87$, $P=0.89$, respectively) (Figures 5D and 5H). In addition, noncystic lung V_T did not significantly correlate to Ti ($P=0.92$) (Figure 5C) or ventilator respiratory rate ($P=0.96$) (Figure 5D).

Figure 5. Correlations of ventilator parameters compared with total lung V_T , regional lung V_T , and individual cystic V_T . (A–D) Total lung V_T (circles), noncystic V_T (squares), and total lung cyst V_T (triangles). (E–H) Large cyst V_T (circles). (A) Correlations of peak inspiratory pressure to total lung V_T (circles; $P=0.027$), total lung cyst V_T (triangles; $P=0.80$), noncystic V_T (squares; $P=0.016$), and (E) large cyst V_T ($P=0.097$) are shown. (B) Correlations of positive end-expiratory pressure to total lung V_T (circles; $P=0.24$), total lung cyst V_T (triangles; $P=0.82$), noncystic V_T (squares; $P=0.19$), and (F) large cyst V_T ($P=0.39$) are shown. (C) Correlations of inspiratory time to total lung V_T (circles; $P=0.57$), total lung cyst V_T (triangles; $P=0.22$), noncystic V_T (squares; $P=0.92$), and (G) large cyst V_T ($P=0.48$) are shown. (D) Correlations of ventilator respiratory rate to total lung V_T (circles; $P=0.86$), total lung cyst V_T (triangles; $P=0.87$), noncystic V_T (squares; $P=0.96$), and (H) large cyst V_T ($P=0.89$) are shown. PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; Resp = respiratory; T_i = inspiratory time; TV = tidal volume.

Discussion

During the progression of sBPD, the lung parenchyma changes from a homogeneous surfactant deficient early phase to a heterogeneous late phase that is characterized by areas of hyperdense and hypodense lung pathology. Our understanding of the heterogeneous nature of sBPD lung disease has been limited by the lack of objective analysis of the regional lung structure and respiratory mechanics. Moreover, this lack of understanding has historically made the ventilatory management of infants in the late phase challenging. The current dogma suggests these older NICU patients are best managed with slow respiratory rate and long T_i . However, our inability to evaluate respiratory mechanics within these heterogeneous regions has limited the production of evidence to support or refute this theory. Through the use of UTE MRI, we objectively analyzed air movement throughout the varying regions of the lung in quiet-breathing, nonsedated infants with sBPD and control subjects.

We compared cyst volumes at end-inspiratory versus end-expiratory stages of the respiratory cycle to first determine if cysts were static or capable of a respiratory V_T . When the total lung cysts were indirectly evaluated by our density-thresholding measurements, there was a measurable V_T that was greater than the normalized V_T of the noncystic lung, suggesting that, in general, the cystic areas of the lung have a greater compliance than noncystic regions. When the larger cysts were directly evaluated, there was also a measurable V_T ; however, the V_T in the larger cysts was quite variable. In general, the larger the individual cyst or the larger the cumulative size of the cysts, the greater the V_T generated. This suggests that most cysts move air, and the air movement increases with increasing cyst size.

Interestingly, about a quarter of the large cysts had a negative V_T . A potential explanation for this finding is that these negative V_T cysts are composed entirely of trapped air and collapse as the surrounding lung expands, increasing pressure on the cysts during normal inhalation. The negative V_T seen could also be a result of pendelluft air movement from one region of the lung to the next rather than a true inspiratory and expiratory V_T . This clinically

can express in mechanical ventilation as lungs beating out of phase but may be happening on the smaller level in the individual cysts, resulting in the appearance of negative V_T s and signifying both a high level of resistance and compliance within the cystic regions of the lung (26–28).

We have previously demonstrated a strong correlation between BPD disease severity and quantifiable MRI structural abnormalities of the lung (16, 29). However, when we used MRI to compare the percentage of lung composed of cyst to the ability to oxygenate (i.e., oxygen saturation/ F_{IO_2} levels), ventilate (i.e., CO_2 levels), or a respiratory severity index (i.e., mean airway pressure $\times F_{IO_2}$), there was only a slight trend correlating cysts with oxygenation. Previous studies have demonstrated an association between the degree of cystic BPD lung disease and the severity of the clinical status (17, 29, 30); therefore, our lack of correlation is unexpected. Because the threshold of clinically significant cystic lung disease is unknown, it is possible our patients were still below that level of lung disease. In addition, it is possible that our markers of disease severity were influenced by other clinical variables and therefore did not represent disease severity in our population. Finally, it is possible that although cysts are a marker of disease severity, they retain some respiratory function. The possibility of cysts retaining function was investigated by our comparison between cyst $\dot{V}_E$ and CO_2 . Although there was no statistically significant correlation between $\dot{V}_E$ of the cystic lung with CO_2 , the slope of total lung cyst $\dot{V}_E$ was nearly identical to the slope of the lung $\dot{V}_E$ versus CO_2 (which was also a nonsignificant trend). Because it is largely accepted and proven that CO_2 levels decrease as the volume of air moved through normal lungs increases, it can be reasoned that absence of statistical significance between lung and cyst V_T

versus CO_2 is more likely because of the variability in our population rather than an inability of normal or cystic lung to remove CO_2 . When considered in tandem, these findings suggest that cysts preserve some level of functionality (i.e., V_T and gas exchange); however, further studies are needed to clearly define the level of contribution of cysts to lung function.

If cysts do retain some functionality, a logical subsequent question is what ventilator parameters increase or decrease air movement through the cystic and noncystic regions of the lung. To address this question, multiple ventilator settings were compared with V_T to assess which variables promoted the greatest air movement in the lungs, total lung cysts, noncystic lung, and large cyst. Our analysis suggests that increases in pressure elevate V_T in noncystic regions of the lung. However, the correlation between cyst V_T and pressure was not observed when we looked exclusively at the large cysts, suggesting there may be a threshold cyst size at which pressure no longer positively influences V_T .

Surprisingly, Ti and ventilator respiratory rates did not significantly correlate with V_T in total lung, total lung cysts, noncystic lung, or large cyst, contrasting with present theories that long Ti and slow respiratory rates are required to move air through the heterogeneous chronic BPD lung.

Although this study allowed for the predominantly objective analysis of infants with sBPD, there were still several factors that could have improved our ability to analyze the effects of sBPD in the late-stage infant lung. The first factor was the limited number of patients and the wide patient-to-patient variability. Because of the critical nature of this patient population, there is a limited number of infant images to be used in the study. A way to overcome patient-to-patient variability would be serial MRI analysis of individual patients before and after changing ventilator settings and

observing the effects on whole lung and regional V_T , but this approach was not feasible in our current cohort. Because of the limited sample size, the results may not apply to all premature infants with BPD because only extreme preterm infants were analyzed in the study. Another limitation of the study was that not every large cyst was measured, instead resorting to a random sampling of cysts in infants with more than nine cysts. However, every cyst was included in the total lung cysts analysis, providing a picture of V_T in all low-density parenchyma in the sBPD infant lung. It is plausible that the density-based method may have included regions of the lung that were hyperinflated rather than truly cystic; however, our density threshold was equivalent to the density of the interior of a large cyst. Therefore, the denser hyperinflated and noncystic regions should have been excluded from the total lung cysts category. Although unlikely, there is a slight chance results were confounded by lack of ventilator setting cohesiveness and because some ventilators are more effective at ventilating certain regions of lung than others. The final limitation of the study was that although UTE MRI allows for regional evaluation of quiet-breathing infant lungs, it does not allow for direct analysis of gas exchange within these regions, instead relying on the correlation between air movement within the lung and clinical factors to draw conclusions about functionality of the heterogeneous nature of the lung.

In summary, the current analysis suggests that areas of cystic sBPD are not merely regions of trapped air but are rather capable of a measurable V_T and may even contribute to pulmonary gas exchange. ■

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

References

1. Abman SH, Bancalari E, Jobe A. The evolution of bronchopulmonary dysplasia after 50 years. *Am J Respir Crit Care Med* 2017;195:421–424.
2. Higgins RD, Jobe AH, Koso-Thomas M, Bancalari E, Viscardi RM, Hartert TV, et al. Bronchopulmonary dysplasia: executive summary of a workshop. *J Pediatr* 2018;197:300–308.
3. Jobe AH. The new bronchopulmonary dysplasia. *Curr Opin Pediatr* 2011;23:167–172.
4. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, et al. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics* 2010;126:443–456.
5. Lal CV, Ambalavanan N. Biomarkers, early diagnosis, and clinical predictors of bronchopulmonary dysplasia. *Clin Perinatol* 2015;42:739–754.
6. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med* 1967;276:357–368.
7. Jobe AH. What is RDS in 2012? *Early Hum Dev* 2012;88:S42–S44.

8. Bhandari A, McGrath-Morrow S. Long-term pulmonary outcomes of patients with bronchopulmonary dysplasia. *Semin Perinatol* 2013;37:132–137.
9. Gibson A-M, Doyle LW. Respiratory outcomes for the tiniest or most immature infants. *Semin Fetal Neonatal Med* 2014;19:105–111.
10. Abman SH, Collaco JM, Shepherd EG, Keszler M, Cuevas-Guaman M, Welty SE, et al. Interdisciplinary care of children with severe bronchopulmonary dysplasia. *J Pediatr* 2017;181:12–28.e1.
11. Aly H, Abdel-Hady H. Respiratory management of newborns. London: IntechOpen; 2016.
12. Higano NS, Hahn AD, Tkach JA, Cao X, Walkup LL, Thomen RP, et al. Retrospective respiratory self-gating and removal of bulk motion in pulmonary UTE MRI of neonates and adults. *Magn Reson Med* 2017;77:1284–1295.
13. Walkup LL, Tkach JA, Higano NS, Thomen RP, Fain SB, Merhar SL, et al. Quantitative magnetic resonance imaging of bronchopulmonary dysplasia in the neonatal intensive care unit environment. *Am J Respir Crit Care Med* 2015;192:1215–1222.
14. Hahn AD, Higano NS, Walkup LL, Thomen RP, Cao X, Merhar SL, et al. Pulmonary MRI of neonates in the intensive care unit using 3D ultrashort echo time and a small footprint MRI system. *J Magn Reson Imaging* 2017;45:463–471.
15. Hatabu H, Alsop DC, Listerud J, Bonnet M, Geftter WB. T2* and proton density measurement of normal human lung parenchyma using submillisecond echo time gradient echo magnetic resonance imaging. *Eur J Radiol* 1999;29:245–252.
16. Higano NS, Fleck RJ, Spielberg DR, Walkup LL, Hahn AD, Thomen RP, et al. Quantification of neonatal lung parenchymal density via ultrashort echo time MRI with comparison to CT. *J Magn Reson Imaging* 2017;46:992–1000.
17. Yoder LM, Higano NS, Schapiro AH, Fleck RJ, Hysinger EB, Bates AJ, et al. Elevated lung volumes in neonates with bronchopulmonary dysplasia measured via MRI. *Pediatr Pulmonol* 2019;54:1311–1318.
18. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The diagnosis of bronchopulmonary dysplasia in very preterm infants: an evidence-based approach. *Am J Respir Crit Care Med* 2019;200:751–759.
19. Johnson KM, Fain SB, Schiebler ML, Nagle S. Optimized 3D ultrashort echo time pulmonary MRI. *Magn Reson Med* 2013;70:1241–1250.
20. Tkach JA, Hillman NH, Jobe AH, Loew W, Pratt RG, Daniels BR, et al. An MRI system for imaging neonates in the NICU: initial feasibility study. *Pediatr Radiol* 2012;42:1347–1356.
21. Tkach JA, Merhar SL, Kline-Fath BM, Pratt RG, Loew WM, Daniels BR, et al. MRI in the neonatal ICU: initial experience using a small-footprint 1.5-T system. *AJR Am J Roentgenol* 2014;202:W95–W105.
22. Tkach JA, Li Y, Pratt RG, Baroch KA, Loew W, Daniels BR, et al. Characterization of acoustic noise in a neonatal intensive care unit MRI system. *Pediatr Radiol* 2014;44:1011–1019.
23. Merhar SL, Tkach JA, Woods JC, South AP, Wiland EL, Rattan MS, et al. Neonatal imaging using an on-site small footprint MR scanner. *Pediatr Radiol* 2017;47:1001–1011.
24. Bates AJ, Higano NS, Hysinger EB, Fleck RJ, Hahn AD, Fain SB, et al. Quantitative assessment of regional dynamic airway collapse in neonates via retrospectively respiratory-gated ¹H ultrashort echo time MRI. *J Magn Reson Imaging* 2019;49:659–667.
25. Hislop AA, Wigglesworth JS, Desai R. Alveolar development in the human fetus and infant. *Early Hum Dev* 1986;13:1–11.
26. Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa EL, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med* 2013;188:1420–1427.
27. Greenblatt EE, Butler JP, Venegas JG, Winkler T. Pendelluft in the bronchial tree. *J Appl Physiol (1985)* 2014;117:979–988.
28. Walkup LL, Roach DJ, Hall CS, Gupta N, Thomen RP, Cleveland ZI, et al. Cyst ventilation heterogeneity and alveolar airspace dilation as early disease markers in lymphangioleiomyomatosis. *Ann Am Thorac Soc* 2019;16:1008–1016.
29. Higano NS, Spielberg DR, Fleck RJ, Schapiro AH, Walkup LL, Hahn AD, et al. Neonatal pulmonary magnetic resonance imaging of bronchopulmonary dysplasia predicts short-term clinical outcomes. *Am J Respir Crit Care Med* 2018;198:1302–1311.
30. Ochiai M, Hikino S, Yabuuchi H, Nakayama H, Sato K, Ohga S, et al. A new scoring system for computed tomography of the chest for assessing the clinical status of bronchopulmonary dysplasia. *J Pediatr* 2008; 152: 90–95.e953.