Infant Pulmonary Function Testing and Phenotypes in Severe Bronchopulmonary Dysplasia

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abstract

BACKGROUND: The definition of severe bronchopulmonary dysplasia (sBPD) is based on respiratory support needs. The management of a patient with sBPD remains empirical and is highly variable among providers. Our objective in this study was to test the hypothesis that infant pulmonary function testing (iPFT) would reveal distinct phenotypes in patients with established sBPD during the initial NICU stay.

METHODS: A prospective cohort study with data prospectively collected on infants with sBPD from May 1, 2003, to June 30, 2016. iPFT data were used to classify the patients as obstructive, restrictive, or mixed.

RESULTS: The median gestational age at birth was 25 weeks (interquartile range [IQR], 24–27 weeks) and the median birth weight was 707 g (IQR, 581–925 g). At the time of iPFT, the median postmenstrual age was 52 weeks (IQR, 45–63 weeks), and the median weight was 4.4 kg (IQR, 3.7–6.0 kg). There were 56 (51%) patients with obstructive, 44 (40%) with mixed, and 10 (9%) with restrictive phenotypes. Moderate or severe obstruction was seen in 86% of the obstructive group and 78% of the mixed group. Of the restrictive patients, 70% had moderate and 30% had mild restriction. Bronchodilator response was seen in 74% of obstructive, 63% of mixed, and 25% of restrictive patients.

CONCLUSIONS: Our findings reveal that sBPD as it is currently defined includes distinct phenotypes. Future researchers of diagnostic approaches to this population should consider the development of bedside tests to define phenotypes, and researchers in future therapeutic trials should consider the use of pulmonary function phenotyping in patient recruitment.

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WHAT'S KNOWN ON THIS SUBJECT: Bronchopulmonary dysplasia (BPD) is the most common morbidity in preterm infants, while pulmonary function testing in surviving children with BPD reveals primarily obstruction; little is known regarding pulmonary function testing abnormalities in infants with BPD during the initial NICU stay.

WHAT THIS STUDY ADDS: In this study of 110 infants with severe BPD, we used pulmonary function testing data during the initial NICU stay at a mean postmenstrual age of 52 weeks and found 3 distinct phenotypes: obstruction, mixed, and (surprisingly) 9% pure restriction.

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Bronchopulmonary dysplasia (BPD) is the most common morbidity in extremely preterm infants.[1] Despite advances in neonatal care that have led to the improved survival of extremely preterm infants, there has been no decrease in the incidence of BPD among survivors.[2] BPD was first described in 1967 by Northway et al.[3] The current definitions of BPD are based on the need for supplemental oxygen at 28 days and/or 36 weeks postmenstrual age (PMA). The National Institutes of Health and Office of Rare Diseases consensus definition of BPD, which was developed in 2001, defines BPD as a requirement for supplemental oxygen for at least 28 days in infants born at <32 weeks' gestation and classifies BPD as mild, moderate, or severe on the basis of the supplemental oxygen and level of respiratory support needed at 36 weeks PMA.[4] Severe BPD (sBPD) is defined as a need for ≥30% supplemental oxygen and/or positive pressure support at 36 weeks PMA.

There is significant practice variation in the approach to sBPD both within an institution and among institutions.[5,6] This lack of standardization in care for patients with sBPD arises from the lack of a good definition for BPD and the widely variable patient presentation and clinical course.[7] Thus, understanding the heterogeneity of sBPD by determining the potential phenotypes in patients with sBPD will pave the way for better therapeutic strategies, modify disease progression, and/or improve the hospital course. There have been pulmonary function studies done in children and young adult survivors of BPD[8,9] as well as preterm patients with developing BPD; however, there are little pulmonary function data in the literature from infants with established sBPD during the initial NICU hospitalization. Therefore, we tested the hypothesis that infant pulmonary function testing (iPFT) would reveal distinct sBPD phenotypes in patients with sBPD during the initial NICU stay.

METHODS

This study was approved by the institutional review board at Nationwide Children's Hospital in Columbus, Ohio, and informed parental consent was obtained from all subjects.

Subjects

Data were prospectively collected on infants who were hospitalized in the NICU with a primary diagnosis of sBPD; were referred for their first iPFT between May 1, 2003, and June 30, 2016; and had been discharged by the time of data analysis. Patients with sBPD who were failing to make significant progress were referred for iPFT, and the decision to refer for iPFT was made by consensus of the multidisciplinary BPD team. We estimate that they represent ~15% of all patients with sBPD admitted during this time frame.

Measurement of Pulmonary Function

All iPFT was performed by using the Infant Pulmonary Laboratory (nSpire Health, Inc, Longmont, CO). If present at the time of iPFT, endotracheal tubes or tracheostomy tubes were replaced with cuffed tubes before testing. Infants were sedated with chloral hydrate and underwent raised-volume rapid thoracic compression spirometry and body plethysmography measurements as previously described.[10–12] The reproducibility of these measurements in our iPFT laboratory have been previously reported, as have the normative data.[10–12] For those in whom bronchodilator responsiveness (BDR) was tested, albuterol was held for 8 hours before testing, and then 2 puffs of albuterol were given every 2 minutes until a 10% increase in heart rate was noted or a maximum of 8 puffs were given, and then the iPFTs were repeated. For this study, we defined BDR as a >10% increase in forced expiratory volume at 0.5 seconds ($FEV_{0.5}$) (percent predicted) as previously described by Goldstein et al.[11] This represents ≥2 SDs above the mean for percent change in $FEV_{0.5}$ in infants, and the coefficient of variation for $FEV_{0.5}$ is 2.2%.[11]

Data Analysis

Pulmonary function data were collected in accordance to American Thoracic Society and European Respiratory Society guidelines,[13] and data for each subject represent 3 measurements within 5% to 10% of each other. Pulmonary function testing data are given as percent of predicted. Secondary outcomes assessed included subject demographics and patient outcomes.

Statistical Analysis

Data are presented as median (interquartile range [IQR]) or percentage unless otherwise specified. The continuous data were not normally distributed, so a Kruskal-Wallis test was used to compare continuous demographic and pulmonary function characteristics, >2 groups were compared with a Dunn's test, which was done post hoc to identify differences among groups. When only 2 groups were compared, a Mann–Whitney rank-sum test was used. A χ^2 test was used to compare categorical outcomes. Selected variables were used in multiple logistic regression modeling. Results from logistic regression are presented as odds ratios (ORs) and 95% confidence intervals (CIs). A P value of <.05 was considered significant. Statistical analysis was performed by using either SAS version 9.3 (SAS Institute, Inc, Cary, NC) or SigmaPlot 12.0 (Jandel Scientific, San Rafael, CA).

RESULTS

There were 110 infants with the primary diagnosis of sBPD who met study inclusion criteria. The demographic data of the entire cohort are given in Table 1. In general, these patients were born extremely preterm and of extremely low birth weight, and thus were at high risk for comorbidities of preterm delivery (Table 1). These patients had relatively long initial NICU hospitalizations (Table 1). The iPFT was done at a median PMA of 52 weeks or a median corrected chronological age of 12 weeks (IQR, 5–23 weeks).

TABLE 1 Demographics of the Entire Cohort

	Median [IQR] or % (*n*/*N*)
Gestational age, wk	25.5 [24.4–27.0]
Birth wt, g	707 [581–925]
SGA	24% (26/107)
Antenatal steroids	83% (90/108)
ETS during pregnancy	35% (37/106)
Family history of asthma	33% (33/101)
IVH	39% (43/110)
Grade 3 or 4 IVH	12% (13/110)
Patent ductus arteriosus ligation	33% (36/110)
Sepsis	30% (33/110)
Necrotizing enterocolitis	5% (6/110)
Ventilator, d	151 [98–294]
Length of stay, d	305 [216–462]
Age at iPFT, wk PMA	52 [45–63]
Wt at iPFT, g	4350 [3652–5972]
Length at iPFT, cm	53 [49.5–59.5]

ETS, environmental tobacco smoke; IVH, intraventricular hemorrhage.

The iPFT data are presented in Table 2. These data were used to classify patients into 1 of 3 phenotypes: (1) obstructive ($FEV_{0.5}$ <80% predicted and total lung capacity [TLC] ≥90% predicted), (2) restrictive (TLC <90% predicted and $FEV_{0.5}$ and/or forced vital capacity [FVC] ≥90% predicted), and (3) mixed (TLC <90% predicted and $FEV_{0.5}$ and/or FVC <90% predicted). By using these criteria, no patients in the obstructive group had any evidence of restriction, whereas no patients in the restrictive group had any evidence of obstruction (Table 2). Using these criteria, we found that 56 patients could be classified as obstructive, 10 as restrictive, and 44 as mixed (Table 2). Although the restrictive and mixed groups tended to have lower compliance of the respiratory system (Crs) than did the obstructive group, these differences did not reach statistical significance. The restrictive and mixed groups had greater forced expiratory flows than did the obstructive group (Table 2). The $FEV_{0.5}$ and/or FVC was significantly greater in the restrictive group than in either the obstructive or mixed groups and was greater in the mixed group than in the obstructive group (Table 2). The lung volumes were significantly lower in both the restrictive and mixed groups than in the obstructive group, and there were no differences between the restrictive and mixed groups in the measured lung volumes (Table 2). As expected, there was no difference in BDR (as it is defined) between the obstructive and mixed groups, whereas there was a significantly lower rate of BDR in the restrictive group than in the obstructive group (Table 2). Patients who had a BDR had a significantly lower $FEV_{0.5}$ prebronchodilator than did those without a BDR (Fig 1).

We then determined if there were differences among patient groups depending on the iPFT-determined phenotype, as shown in Table 3. There were no significant differences between the groups in gestational age at birth, sex, race, antenatal steroid exposure, prenatal tobacco exposure, or family history of asthma. The patients in the restrictive group had significantly lower birth weight than did obstructive patients. There were no differences in the groups regarding respiratory support needs at 36 weeks, the timing of the iPFT, or either weight or length at the time of iPFT. Significantly more patients in the restrictive group had noninvasive support at the time of iPFT than in the other 2 groups. There was a tendency for more of the patients with obstruction to have a tracheostomy in place at the time of iPFT. The patients in the obstructive group had strikingly more ventilator days after the iPFT (P = .001) than did patients in the mixed group. There were no significant differences in NICU outcome measures among the groups. It should be noted that in this cohort of patients with sBPD, the survival rate for the entire cohort was 94% and did not differ among groups.

For the next analysis, given the relatively small number of patients with pure restriction, we combined the restrictive group and mixed group (R+M). We used 7 of the first 8 data points from Table 3, which would have been available at the time of birth, in multiple logistic regression modeling to determine if there were any factors that were associated with the development of the R+M phenotype in patients with sBPD (Table 4). Given that patients in the R+M group had a milder course with a shorter duration of mechanical ventilation after iPFT, we felt it would be important for disease progression to try to identify early factors associated with the development of the R+M phenotype in patients with sBPD. Because birth weight and small for gestational age (SGA) are related, we opted to use SGA in the model. In this cohort, only SGA had a small (but statistically significant) association with the R+M phenotype (OR 3.58 [95% CI, 1.23–10.45]; P = .02).

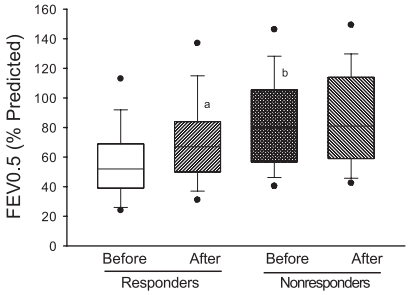

FIGURE 1

The $FEV_{0.5}$ as a percent of predicted before and after albuterol in responders (n = 59) and nonresponders (n = 36). [a] Postbronchodilator use is different from prebronchodilator use in the same group (P < .05). [b] Prebronchodilator nonresponders are different from prebronchodilator responders (P < .05).

DISCUSSION

In this study, we demonstrate that there are 3 distinct iPFT phenotypes in patients who are diagnosed with sBPD and were studied at a median corrected age of 12 weeks (IQR, 5–23 weeks) during their initial NICU stay. These results reveal distinct phenotypes within the current definition of sBPD that may help differentiate patients with sBPD and have implications for therapy. Thus, the findings are consistent with our hypothesis, and we suggest that phenotyping patients with sBPD may lead to improved outcomes for patients with sBPD by allowing for the development of specific and rational therapies.

We found that the vast majority of patients with sBPD who were referred for iPFT had some element of obstruction, and this result is consistent with previous reports of patients with BPD who were studied during the NICU period. In an early report, Baraldi et al[14] found that in a small cohort of infants born at ≤1250 g who developed BPD, resistance of the respiratory system (Rrs) was higher at 6 months of age than in normative data and that all infants demonstrated some degree of flow limitation at repeat testing at 2 years of age. In a more recent cohort[15] that included 43 extremely preterm infants studied at 7 ± 6 months of age, researchers found that these infants had airflow obstruction. Schmalisch et al[16] studied 186 infants born at <28 weeks' gestation with the diagnosis of severe neonatal lung disease, which was defined as needing mechanical ventilation for >24 hours at 52 ± 11 weeks, and found that they exhibited airflow obstruction, although it should be pointed out that most of these patients would not likely have had the diagnosis of sBPD as defined herein. Filbrun et al[17] reported on a slightly older (59 ± 18 weeks) cohort of patients who were relatively well and found that even this group of infants demonstrated airflow obstruction. Robin et al[18] reported similar results in a cohort of 28 infants with BPD who were studied at 68 ± 36 weeks of age. Thus, although the majority of patients in the cohorts studied previously would not have met the definition of sBPD, taken together, these data reveal that most preterm infants with BPD have evidence of airflow obstruction at the time of iPFT. Our data reveal that 91% of infants with sBPD during the initial NICU stay have an obstructive component to their phenotypes, with 51% of patients with sBPD having the purely obstructive phenotype.

Interestingly and importantly, we found that a small but significant portion of patients had purely restrictive disease. We could find no previous reports of preterm infants with sBPD studied during the initial NICU stay in which researchers specifically reported a purely restrictive phenotype. The presence of a purely restrictive phenotype has

TABLE 2 iPFT Results by Pathophysiologic Classification

	Entire Cohort, Median [IQR] or % (*n*/*N*)	Obstructive, Median [IQR] or % (*n*/*N*)	Restrictive, Median [IQR] or % (*n*/*N*)	Mixed, Median [IQR] or % (*n*/*N*)	*P*
Distribution	—	51% (56/110)	9% (10/110)	40% (44/110)	—
Crs, % predicted	69 [49–93]	73 [52–96]	64 [48–69]	67 [47–89]	.24
FVC, % predicted	77 [62–93]	89 [75–106]	61 [60–67][a]	70 [60–81][a]	<.001
$FEV_{0.5}$, % predicted	46 [39–57]	43 [35–53]	59 [57–62][b]	46 [40–57][c]	.002
$FEV_{0.5}$ and/or FVC, % predicted	64 [48–79]	49 [39–69]	94 [91–97][a]	69 [59–79][b,c]	<.001
$FEF_{50\%}$, % predicted	20 [11–42]	12 [8–21]	74 [53–90][a]	24 [15–42][b,d]	<.001
$FEF_{75\%}$, % predicted	13 [7–26]	8 [6–16]	49 [40–82][a]	16 [9–25]	<.001
$FEF_{85\%}$, % predicted	11 [7–22]	8 [6–15]	42 [34–58][a]	14 [8–19.7][b,d]	<.001
$FEF_{25\%–75\%}$, % predicted	16 [9–36]	11 [7–18]	71 [55–82][a]	21 [13–36][b,d]	<.001
TLC, % predicted	91 [76–120]	120 [106–138]	72 [67–78][b]	78 [68–84][b]	<.001
FRC, % predicted	101 [67–144]	141 [104–173]	69 [53–96][b]	67 [59–92][b]	<.001
RV, % predicted	110 [73–169]	165 [122–189]	75 [63–112][b]	72 [55–97][b]	<.001
FRC and/or TLC, % predicted	114 [101–137]	127 [108–145]	108 [93–129][b]	109 [95–121][b]	.002
RV and/or TLC, % predicted	121 [105–150]	134 [119–162]	116 [105–146][b]	109 [94–133][a]	<.001
Degree of restriction (mild or moderate)	49% (54/110)	0% (0/56)	100% (10/10)[a]	100% (44/44)[a]	<.001
Degree of obstruction (moderate or severe)	75% (82/110)	86% (48/56)	0% (0/10)[a]	78% (34/44)[d]	<.001
BDR[e]	66% (61/93)	74% (35/47)	25% (2/8)[b]	63% (24/38)	.02

N = 56, 10, and 44, respectively, for all data except Crs, for which *N* = 48, 5, and 32, respectively. Symbols refer to *P* values from Dunn's post hoc test or direct comparisons using the χ^2 test. $FEF_{25\%–75\%}$, forced expiratory flow midexpiratory phase; $FEF_{50\%}$, forced expiratory flow 50; $FEF_{75\%}$, forced expiratory flow 75; $FEF_{85\%}$, forced expiratory flow 85; FRC, functional residual capacity; RV, residual volume; —, not applicable.

[a] Different from obstructive; P < .001.

[b] Different from obstructive; P < .05.

[c] Different from restrictive; P < .05.

[d] Different from restrictive; P < .001.

[e] P value refers to the result of 1-way analysis of variance or a χ^2 test comparing all 3 groups.

TABLE 3 Patient Characteristics

	Obstructive, Median [IQR] or % (*n*/*N*)	Restrictive, Median [IQR] or % (*n*/*N*)	Mixed, Median [IQR] or % (*n*/*N*)	*P*
Demographics				
African American race	27% (15/56)	50% (5/10)	30% (13/44)	.33
Female sex	37% (21/56)	70% (7/10)	41% (18/44)	.16
Gestational age, wk	25.6 [24.6–27.1]	24.9 [23.6–26.6]	25.1 [24.1–27.1]	.26
Birth wt, g	748 [622–962]	619 [475–675]	687 [570–860]	.04
SGA	18% (10/56)	40% (4/10)	27% (12/44)	.18
Antenatal steroids	84% (47/55)	70%	84% (36/43)	.48
ETS during pregnancy	30% (16/53)	67%	34% (15/44)	.06
Immediate FH of asthma	30% (15/50)	12%	40% (17/43)	.28
36-wk status				
On positive pressure	100% (51/51)	90% (9/10)	98% (41/42)	.49
F_{IO_2}	0.52 [0.43–0.65]	0.53 [0.39–0.71]	0.53 [0.41–0.70]	.91
RSS, MAP × F_{IO_2}	6.9 [4.3–8.9]	8.2 [5.8–9.9]	6.5 [4.0–9.3]	.79
Status at or after iPFT				
PMA, wk	53 [45–63]	65 [48–77]	50 [44–58]	.21
Wt, kg	4.5 [3.7–5.9]	5.7 [4.2–7.0]	4.2 [3.5–5.5]	.23
Length, cm	55 [50–59]	57 [51–63]	52 [49–58]	.27
Noninvasive support	38% (21/56)	90% (9/10)	41% (18/44)	.008
Endotracheal tube	21% (12/56)	0% (0/10)	34% (15/44)	.06
Tracheostomy	41% (23/56)	10% (1/10)	25% (11/44)	.07
Tracheostomy after iPFT	7% (4/56)	0% (0/10)	2% (1/44)	.62
Ventilator d after iPFT	117 [59–308]	20 (*n* = 1)	40 [15–65]	.001[a]
NICU outcomes				
NEC	7% (4/56)	10% (1/10)	2% (1/44)	.27
Grade 3 or 4 IVH	16% (9/56)	20% (2/10)	5% (2/44)	.10
Sepsis	32% (18/56)	40% (4/10)	25% (11/44)	.55
PDA ligation	32% (18/56)	10% (1/10)	39% (17/44)	.22
Discharge outcomes				
Survival	91% (51/56)	100% (10/10)	95% (42/44)	.61
LOS, d	338 [218–484]	312 [222–450]	288 [212–414]	.27
LOS survivors, d	323 [211–483]	312 [222–450]	288 [215–408]	.44
Discharged on ventilator	14% (8/56)	0% (0/10)	2% (1/44)	.08
Ventilator days	204 [100–431]	111 [78–160]	149 [102–224]	.12
Ventilator days survivors	187 [74–410]	111 [78–160]	146 [98–208]	.28

ETS, environmental tobacco smoke; FH, family history; F_{IO_2}, fraction of inspired oxygen; IVH, intraventricular hemorrhage; LOS, length of stay; MAP, mean airway pressure; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; RSS, respiratory severity score.

[a] Restrictive *n* = 1, so it was not included in the statistical analysis.

TABLE 4 Logistic Regression Modeling

Variable	OR	95% CI	*P*
Gestational age, wk	1.20	0.90–1.59	.22
SGA	3.58	1.23–10.45	.02
Sex	0.72	0.30–1.72	.46
African American race	1.33	0.52–3.39	.56
Antenatal steroids	0.79	0.23–2.79	.72
Family history of asthma	1.50	0.60–3.77	.39
ETS during pregnancy	1.93	0.75–4.96	.17

Data available at birth were used in multiple logistic regression modeling to determine potential factors associated with the development of the R+M phenotype in patients with sBPD. ETS, environmental tobacco smoke.

implications for the care of the infant with sBPD. For example, infants with purely restrictive disease are more likely to respond clinically to removal from positive pressure ventilation rather than an approach that includes mechanical ventilation with large tidal volumes and a slow rate aimed at classic BPD with a component of obstruction.[19] This is borne in our finding that only 1 of the 10 patients with the purely restrictive disease required mechanical ventilation after iPFT and then only for 20 days after the iPFT study was done. Contrast this to a median of 117 ventilator days after the iPFT study in the purely obstructive group of patients. Furthermore, 9 of the 10 purely restrictive patients with sBPD were receiving noninvasive support at the time of iPFT compared with only 38% of the purely obstructive group. Thus, the identification of the infants with sBPD and purely restrictive lung disease may be useful in guiding therapy, and the respiratory support that the patients with sBPD with restrictive disease require may be different from that required by the patients with sBPD with obstructive disease.

We also found that 40% of patients had a mixed phenotype. Choukroun et al[20] reported that at 8 years of age in 14 patients who survived sBPD, 2 had a mixed phenotype. Filbrun et al[17] found that the average TLC was 83% ± 14% of predicted in their cohort of 18 patients with BPD, suggesting that at least some patients had a mixed phenotype. Similarly, in the cohort reported by Robin et al,[18] the TLC had a range of 69% to 128% of predicted, again revealing that at least some patients had a mixed phenotype. In our study, the mixed phenotype had substantially fewer ventilator days after iPFT than did the purely obstructive group. This finding again reveals that the approach and outcomes of mechanical ventilation in patients with sBPD may be influenced by the phenotype identified at the time of iPFT.

We attempted to use the data on hand to develop predictive models for the development of the R+M phenotype in patients with sBPD. Because essentially all of these patients with sBPD were on positive pressure at 36 weeks, we used the parameters that would be known at the time of birth to see if there was any association with the R+M phenotype. The only variable that was associated with the development of the R+M phenotype in patients with sBPD by

using logistic regression modeling was SGA status. These findings reveal that the R+M phenotype is more likely in preterm infants with less intrauterine weight gain and is an area that should receive further study related to lung growth and the potential presence of lung hypoplasia. Various biomarkers have been associated with the subsequent development of BPD in preterm infants,[21] although to the best of our knowledge, biomarkers associated with a particular iPFT phenotype in sBPD have not been described.

BDR was seen in 66% of the 93 patients in whom BDR was assessed. Morrow et al[22] demonstrated that in 40 very low birth weight infants studied at 35 weeks corrected age, 53% responded to albuterol with a ≥10% decrease in Rrs. Filbrun et al[17] found that in infants with BPD studied at an average age of 58 weeks (our patients were on average 31 weeks old at the time of study), 40% had BDR as defined by a >24% change in forced expiratory flow 75. Interestingly, we found that patients with sBPD who responded to bronchodilators had a significantly lower $FEV_{0.5}$ prebronchodilator than did the patients who did not respond to bronchodilators. Researchers in a recent meta-analysis[23] examining bronchodilators for the prevention and treatment of chronic lung disease in preterm infants could find no eligible trials in which researchers examined bronchodilators for the treatment of individuals with chronic lung disease (defined by the authors as supplemental oxygen at 28 days of life or 36 weeks PMA in preterm infants). Researchers in another recent, systematic review found only 5 articles out of 181 assessed in which researchers describe responses to inhaled bronchodilators in BPD, and all 5 articles included descriptions of responses to a single dose; in fact, researchers in only 2 of the 5 articles examined physiologic responses, and both studies revealed an improvement in Crs and Rrs.[24] Our data reveal that there is a subgroup of patients with sBPD who respond to bronchodilators. Therefore, we suggest that a randomized controlled trial using baseline $FEV_{0.5}$ as an entry criterion is needed to determine the long-term benefits of bronchodilator therapy in those patients with sBPD who are most likely to respond to bronchodilators.

There are some limitations to our study that should be considered. First, the cohort does not include all patients with sBPD who were admitted to our BPD service during the time frame of the study but only those who were referred for iPFT. In our institution, patients are referred for iPFT when they are not on a clinical trajectory that is suggestive of continued, slow, and steady improvement. Thus, the cohort certainly includes those patients with the severest forms of BPD.[19] Second, there is a relatively small amount of missing iPFT data. However, our cohort is the largest cohort of patients with sBPD during the initial NICU hospitalization that has been reported.

CONCLUSIONS

Patients with sBPD demonstrated 3 distinct iPFT phenotypes: obstructive, restrictive, and mixed. The obstructive phenotype was the most prevalent and was associated with greater birth weight. Although seen in only 9% of patients with sBPD, the purely restrictive phenotype and its diagnosis may be important from a therapeutic prospective because these patients can likely be weaned relatively quickly from positive pressure, and none of the purely restrictive patients were discharged from the hospital on mechanical ventilation. All 3 phenotypes revealed a subset of patients who responded to bronchodilator therapy, and responders had a lower $FEV_{0.5}$ at baseline than did nonresponders. Our findings reveal that sBPD as it is currently defined includes different phenotypes that may require different therapeutic approaches. In patients with sBPD who are not clinically improving, we would suggest that iPFT may be considered to determine their phenotypes to help guide ongoing therapies. Given that most NICUs do not have access to a pulmonary function testing laboratory, in the long-term, it would be helpful to develop easier bedside testing to differentiate these phenotypes, and we suggest that this should be a focused area of future research. Finally, the iPFT for phenotypes could also be used to direct future therapeutic trials in patients with sBPD.

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ABBREVIATIONS

BDR: bronchodilator responsiveness
BPD: bronchopulmonary dysplasia
CI: confidence interval
Crs: compliance of the respiratory system
$FEV_{0.5}$: forced expiratory volume at 0.5 seconds
FVC: forced vital capacity
iPFT: infant pulmonary function testing
IQR: interquartile range
OR: odds ratio
PMA: postmenstrual age
Rrs: resistance of the respiratory system
R+M: restrictive group and mixed group
sBPD: severe bronchopulmonary dysplasia
SGA: small for gestational age
TLC: total lung capacity

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