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Original Research Article

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Please cite this article as: Nelin LD, Kielt MJ, Jebbia M, *et al*. Bronchodilator responsiveness and dysanapsis in bronchopulmonary dysplasia. *ERJ Open Res* 2022; in press (https://doi.org/10.1183/23120541.00682-2021).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

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Bronchodilator Responsiveness and Dysanapsis in Bronchopulmonary Dysplasia

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Take home summary

In 93 BPD patients, 63% were responsive to bronchodilators and responders had significantly lower FEV0.5 and greater hyperinflation than did non-responders. The dysanapsis ratio in responders was significantly smaller than in non-responders.

ABSTRACT

Question addressed: The incidence of bronchopulmonary dysplasia (BPD) following preterm birth is increasing. Bronchodilators are often used to treat patients with BPD with little evidence to guide therapy. To test the hypothesis that there are infant pulmonary function test (iPFT) parameters that can predict subsequent bronchodilator response in infants with BPD.

Methods: Subjects in this study are part of a patient group in whom we reported 3 BPD phenotypes (obstructive, restrictive and mixed) based on iPFT data. From that group, a cohort of 93 patients with iPFT data including bronchodilator response were eligible for this study.

Results: Bronchodilator responsiveness was found in 59 (63%) of the cohort. There were no differences in demographics between the responders and non-responders. There was no difference in forced vital capacity (FVC) between the two groups. Responders had significantly lower $FEV_{0.5}$ and $FEV_{0.5}$/FVC ($p<0.005$) and greater indices of hyperinflation than did non-responders ($p<0.005$). Logistic regression modeling found that pre-bronchodilator $FEV_{0.5}$ and FRC/TLC were significantly associated with bronchodilator response. The magnitude of response to bronchodilators was negatively correlated ($R = –0.49$; $R^2 = 0.24$; $p<0.001$) with the $FEV_{0.5}$. The median dysanapsis ratio in responders (0.08; 95% CI 0.05 – 0.19) was significantly ($p = 0.005$) smaller than in non-responders (0.18; 95% CI 0.06 – 0.38).

Answer to the question: These findings demonstrate that there are pulmonary function test parameters associated with bronchodilator response. Responders had evidence of greater dysanaptic lung growth than do non-responders.

Key Words: Lung diseases, obstructive; infant pulmonary function test; preterm infant

INTRODUCTION

Bronchopulmonary dysplasia (BPD) was first described by Northway in 1967 and is now the most common morbidity following preterm birth with an incidence that is increasing (1,2,3). A recent definition of BPD based on respiratory support at 36 weeks post menstrual age (PMA) divides BPD into 3 grades: Grade 1 low-flow nasal cannula, Grade 2 non-invasive positive pressure, and Grade 3 invasive positive pressure (4). There is little high-grade evidence to support therapeutic approaches in patients with BPD, despite this lack of evidence patients with BPD are often treated with bronchodilators (5,6). However, the use of bronchodilators in BPD is extremely variable between providers and between centers (7,8).

Pulmonary function studies have been reported in children and young adult survivors of BPD (9,10,11) as well as in preterm infants developing BPD (12). However, there is little pulmonary function data from infants with established BPD during their Neonatal Intensive Care Unit (NICU) hospitalization. We recently described a cohort of patients with BPD who had infant pulmonary function testing (iPFT) done during their NICU hospitalization and found that the iPFT data divided the patients into 3 phenotypes: obstructive, restrictive, and mixed (13). We also reported (13) that in those infants tested for bronchodilator responsiveness (BDR), 66% had BDR and those with BDR had a lower pre-bronchodilator (pre-BD) forced expiratory volume in 0.5 seconds ($FEV_{0.5}$). This finding led us to hypothesize that iPFT parameters can be used to predict BDR in infants with established BPD during their NICU hospitalization.

Modeling the airways as tubes and using Pouiselle's Law suggests that airway diameter has the greatest effect on airway resistance and the smallest airways have the greatest resistance (14). It has been shown even in young children and infants without lung disease that peripheral airways have high resistance, and that there is a marked decrease in resistance at 4 to 5 years of

age (15). Dysanaptic lung growth refers to the non-proportional growth of airways and lung resulting in relatively small airways for lung size (16). It has been suggested that the dysanapsis ratio (DR) can be used as a non-invasive method of describing the relationship between airway caliber and lung size, where the smaller the DR the greater the dysanaptic lung growth (17). The DR has been shown in adults to be a predictor of expiratory flow limitation (EFL) (18,19). To the best of our knowledge no one has examined the DR in relation to BDR in infants with established BPD. Therefore, we tested the hypothesis in these infants with BPD and assessment of BDR, that those with BDR would have a smaller DR than would non-responders. In other words, infants with BDR would have relatively smaller airways relative to their lung size than would non-responsive infants.

METHODS

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

Subjects: The subjects in this cohort are the sub-set of a cohort that was described in our recent publication (13) who had BDR testing done. Briefly, data were collected from infants hospitalized in the NICU with a primary diagnosis of BPD who were referred for their first iPFT from May 1, 2003 to October 8, 2015. In our BPD unit, patients are referred for iPFT when they fail to make significant progress; and the decision to refer for iPFT was made by consensus of the multi-disciplinary BPD team. We estimate that the cohort represents ~15% of the all BPD patients admitted to our BPD unit during this time frame.

Infant Pulmonary Function Testing (iPFT): All iPFTs were performed utilizing 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 prior to testing. Infants were sedated with chloral hydrate and underwent raised volume rapid thoracic compression spirometry and body plethysmography measurements as previously described (13,20,21,22). The reproducibility of these measurements in our iPFT laboratory have been previously reported, as have the normative data (20,21,22).

Bronchodilator (BD) responsiveness (BDR) testing: Albuterol was held for 8 hours prior to testing. After pre-BD iPFTs were completed, 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 $FEV_{0.5}$ (percent predicted) as previously described by Goldstein et al. (21), which represents ≥2 standard deviations above the normative mean for change in $FEV_{0.5}$ in infants. The coefficient of variation for $FEV_{0.5}$ is 2.2% (21).

Dysanapsis ratio (DR): The DR is calculated as $FEF_{50}/(FVC \times Pst(l)_{50})$ (19), where FEF_{50} is the forced expiratory flow at 50% of forced vital capacity (FVC), and $Pst(l)_{50}$ is the static recoil pressure at 50% of FVC. We used data from Turner et al. (23) to extrapolate $Pst(l)_{50}$ based on the equation, $Pst(l)_{50} = -0.056 \times \text{age (years)} + 6.3038$ as previously described in both adults (18,19) and children (24). The DR is inversely related to dysanaptic lung growth, i.e. the smaller the DR the more dysanapsis.

Data Analysis: Pulmonary function data were collected in accordance with ATS/ERS Guidelines (25), and for each subject represent 3 measurements within 5-10% of each other. iPFT data are given as percent of predicted. Data was also collected on subject demographics and outcomes.

Statistical Analysis: Data are presented as median and interquartile range [IQR] or number and percentage (%). The continuous data was compared between groups using a Mann-Whitney U test (Sigmaplot 14.0, Jandel Scientific, Carlsbad, CA). A Fisher's Exact Test was used to compare categorical data between groups (GraphPad Prism 8, San Diego, CA). Selected variables were used in multiple logistic regression modeling (Sigmaplot) and results presented as odds ratio (OR) and 95% confidence interval (95% CI). The area under the receiver operating characteristic curve (AUROC) was calculated for selected variables (GraphPad). Linear regression modeling was used for some data pairs (Sigmaplot). A p-value of <0.05 was considered significant.

RESULTS

There were 93 patients with BDR testing; 59 (63%) met criteria for BDR and were termed responders the remaining 34 (37%) were termed non-responders. There were no differences in any of the demographic variables between the two groups as shown in Table 1. Importantly, at the time of iPFT there were no differences between the 2 groups in terms of post-menstrual age (PMA), length, weight, or type of respiratory support. The majority of infants (62%) had Grade 3 BPD, 24% had Grade 2 BPD, and 2% had Grade 1 BPD. An additional 9 (11%) infants lacked reliable respiratory support data at 36 weeks PMA and were therefore non-classifiable.

The pre-BD iPFT results are shown in Table 2. There were 47 (51%) infants classified as obstructive ($FEV_{0.5}$ <80% predicted and TLC ≥90% predicted), 38 (41%) classified as mixed (TLC <90% predicted and $FEV_{0.5}$/FVC <90% predicted), and 8 (9%) classified as restrictive (TLC <90% predicted and $FEV_{0.5}$/FVC ≥90% predicted). There were more infants with

moderate/severe obstruction in the responder group than in non-responder group. Responders had lower $FEV_{0.5}$ and $FEV_{0.5}$/FVC than did non-responders. Responders had greater indices of hyperinflation on iPFT (RV/TLC and FRC/TLC) than did non-responders.

The expiratory flows or indices of hyperinflation from the pre-BD iPFTs that were significantly different between responders and non-responders were used in multiple logistic regression models. To avoid over-fitting our models we examined flows (parameters = 7) and indices of hyperinflation (parameters = 6) separately, and included PMA, length, and weight at time of iPFT in the models. When pre-BD expiratory flows were used in the logistic regression model, only pre-BD $FEV_{0.5}$ was significantly associated with BDR (Table 3). When the indices of hyperinflation were used in the logistic regression model, only pre-BD FRC/TLC was associated with BDR (Table 3). The AUROC for pre-BD $FEV_{0.5}$, FEF_{50} and FRC/TLC are given in Table 4.

To determine if the magnitude of BDR in responders was related to pre-BD flows, hyperinflation, or both we examined the magnitude of BDR as given by the change in $FEV_{0.5}$ pre-BD to post-BD in responders. The median magnitude of BDR in the 59 responder patients was 26% [IQR, 19 – 39]. The magnitude of BDR in the responders was negatively correlated with the pre-BD $FEV_{0.5}$ (Figure 1). The magnitude of BDR in responders was not correlated with the pre-BD FRC/TLC ($R=0.21$; $R^2=0.04$; $p=0.11$).

The median DR in responders was significantly smaller than the median DR in non-responders (Figure 2A), suggesting greater dysanaptic lung growth in responders compared to non-responders. Since we were using an algorithm for calculating $Pst(l)_{50}$ that used age in years and given that our range of ages in years was quite narrow (0.23 – 1.91 years), we examined the relationship between DR and chronological age in years for the entire cohort and found no

significant correlation by linear regression (R = 0.11; R^2 = 0.01; p = 0.31). There was also no correlation between DR and PMA (in weeks) (R = 0.12; R^2 = 0.01; p = 0.27). Examining the relationship between DR and $FEV_{0.5}$ using linear regression we found a significant correlation (Figure 2B). We also examined the relationship of DR to TLC using linear regression and found a significant negative correlation (Figure 2C). Using multiple logistic regression modeling and including PMA, length, and weight at time of iPFT, DR predicted BDR with an OR of 0.011 (95% CI 0.001 – 0.195; p = 0.002) (Table 3).

There were no differences in outcomes between the 2 groups as shown in Table 5.

DISCUSSION

This study demonstrates that in a cohort of Neonatal ICU patients with BPD referred for iPFT, the majority of whom had Grade 3 BPD, 63% were responsive to bronchodilators. There were no demographic differences between responders and non-responders in this cohort of infants. We did find that pre-BD values for $FEV_{0.5}$ and FEF_{50} were lower in responders than in non-responders, with more hyperinflation as assessed by RV/TLC and FRC/TLC on the iPFT in responders than in non-responders. Indeed, the $FEV_{0.5}$ and FRC/TLC were modestly predictive of BDR in this cohort using logistic regression modeling and AUROC analysis.

Infants in this cohort all had BPD and all, but 2 subjects, had either Grade 2 or Grade 3 BPD. Even in this population where 91% had obstruction, 37% of the subjects were non-responsive to bronchodilators. The cohort is not a consecutive cohort of all patients with Grade 2 or Grade 3 BPD, but rather infants chosen for iPFT based on failing to have a clinical response to usual therapy. Several studies examined BDR in older children or young adults who had BPD (9,10,11), although there are very few published studies examining BDR using iPFT in BPD

infants during their initial NICU hospitalization. Morrow et al. (26) evaluated 40 preterm infants with evolving BPD with iPFTs at a mean PMA of 35 weeks and found that 65% had a response to bronchodilators, and responders tended to have a greater baseline respiratory system resistance (R_{RS}) than non-responders (26), consistent with our findings that responders tended to have a lower $FEV_{0.5}$ than did non-responders. Robin et al. (27) evaluated 17 infants with BPD at a mean post-natal age of 68 weeks (our cohort had a mean post-natal age of 30 weeks) and found that 35% had significant bronchodilator responsiveness (defined as a change in FEF_{75} >24.3%). Furthermore, they reported that responders had significantly lower baseline FEF_{75} than did non-responders (27); again consistent with our findings. Together with our data, these findings support the notion that not all patients with established BPD have BDR and that patients with greater obstruction at baseline are more likely to demonstrate BDR.

Responders had more hyperinflation on iPFT than did non-responders, as evidenced by larger RV/TLC and FRC/TLC ratios as well as smaller VC. It has been shown that infants with BPD have greater RV/TLC than do infants without BPD (27). Recently, Yoder et al. (28) used MRI to measure FRC in NICU patients at PMA between 35-42 weeks and found that subjects with severe BPD had significantly greater FRC than did subjects with mild BPD. Dassios et al. (29) found that the greater the degree of hyperinflation in preterm infants (studied at a median of 6 weeks of age) the greater the ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch. To the best of our knowledge we are the first to describe in a cohort of patients all with BPD that there are measurable differences in hyperinflation, with more hyperinflation in those infants that respond to bronchodilators than in those that don't respond. In adults with COPD it has also been reported that patients with lung hyperinflation have better bronchodilator responsiveness (30). These findings suggest that the degree of hyperinflation may underlie BDR in BPD and further

studies are needed examining biomarkers of hyperinflation in relation to BDR. These findings also raise the question of whether bronchoconstriction is involved in the mechanism underlying hyperinflation in BPD?

We didn't find evidence of a pre-BD $FEV_{0.5}$ cut-off value for predicting BDR, but there was a negative correlation between the magnitude of BDR and $FEV_{0.5}$. While the lung volume parameters, FRC/TLC and RV/TLC, were not significantly correlated with the magnitude of BDR. These findings have potential implications for precision therapeutics in BPD. Multi-center studies have shown extreme variability in bronchodilator use in patients with severe BPD (5-8), which suggests a lack of high-quality evidence to support the precise utilization of bronchodilators targeting those patients who may benefit from the medication. In our unit, these patients are treated with bronchodilators. Our findings demonstrate that not all infants with severe BPD are BDR, which may lead clinicians to use other criteria (i.e., physical exam, changes in delivered tidal volumes or pressures on the ventilator, tolerance of therapies, etc.) that are not standardized to guide their use of bronchodilators. Our findings also suggest that iPFT data can predict BDR in the most severe forms of BPD. It should be remembered that though bronchodilators are widely used and generally considered safe in BPD patients, bronchodilators are not without risk (31,32). Targeting the use of bronchodilators to BPD patients with physiologic evidence of expiratory flow limitation on iPFT may be one way to optimize therapeutic effect while avoiding medication side effects.

The mechanisms underlying bronchoconstriction and bronchodilator responsiveness in patients with BPD are likely to be very complex and multi-factorial; and understanding exactly the mechanisms involved in this cohort are beyond the scope of this study or any single study. However, we did wonder how lung growth and particularly dysanaptic lung growth might affect

BDR in established BPD in patients still in the NICU. We found in this cohort of BPD patients that the DR was smaller in responders than in non-responders suggesting that BPD patients with BDR likely have relatively smaller airways in proportion to their lung size than do non-responders. Duke, et al. (19) reported in adult survivors of preterm birth that those with BPD had smaller DR than adult survivors of preterm birth without BPD, and that the DR was significantly correlated with peak expiratory airflow at rest and the extent of EFL during exercise. This suggests that at least some of the BD response in the responder group may be due to their relatively smaller airways in relation to lung size. Another way to think of this is that in patients with lower DR the relatively smaller airways in relation to lung size would be more likely to have a measurable change in iPFT parameters following BD administration. Furthermore, patients with smaller DR would be expected to have lower $FEV_{0.5}$ and FEF_{50} due to the relatively higher airway resistance, and we found a direct correlation between DR and $FEV_{0.5}$ in this cohort. The relationship between DR and $FEV_{0.5}$ also suggests that dysanaptic airway development underlies at least some of the BDR seen in the responder group in this cohort of NICU patients with BPD. The findings that DR was correlated with TLC and that the patients with the largest TLC (i.e. the greatest amount of hyperinflation) had the lowest DR, may suggest that dysanaptic lung growth also contributes to the hyperinflation seen in patients with severe BPD. Further studies are needed examining dysanaptic lung growth in BPD. It would be interesting to examine for instance whether DR increases with good somatic growth, i.e. if airway caliber increases relatively more than lung size increases as the lung grows, and whether this is a mechanism for the improvement in lung function seen in established BPD with good linear growth.

There are some limitations to this study that should be noted. First, it is not a consecutive cohort of subjects, and thus not a true epidemiological assessment of BDR in BPD. However, as far as we know this is the largest cohort of BPD infants with BDR testing during the initial NICU hospitalization. Another aspect of this is that the patients studied represent the severest forms of BPD since the patients were referred if they were not responding as expected. Thus, these data may not be widely generalizable to all BPD. Second, to obtain the measurement of DR we used static recoil pressures at 50% of lung volume ($Pst(l)_{50}$) extrapolated from adult values (23) as has been previously described (18,19,24). However, given the lung growth that occurs from birth through early childhood the assumption of a linear relationship of $Pst(l)_{50}$ values with age in early childhood may not be entirely valid (15). However, despite this limitation we were able to find differences in DR between infants, expected correlations with other iPFT parameters, and no significant correlation between DR and age in this cohort. A third potential limitation might be that we were unable to correlate our iPFT findings with either thorough physical exam data or rigorous imaging data. Another potential limitation is that iPFT is not widely available in this age range of patients. However, with advances in ventilator technology, ventilators now provide in-line measurements of at least some aspects of pulmonary function and there continues to be the development of new ways of measuring pulmonary function in this age group (such as forced oscillometry, MRI, etc.). Finally, the parameters studied here to predict BDR were only moderately predictive using AUROC analysis, thus further studies to find better predictive tests for BDR are required, and these predictive lung function tests should include parameters readily available to the clinician.

CONCLUSION

We found in a cohort of patients with BPD that most, but not all, were responsive to bronchodilators. The measured iPFT parameters associated with BDR in this cohort were $FEV_{0.5}$ and FRC/TLC ratio. Our results suggest that future studies are needed to better predict BDR in patients with BPD. Interestingly, the group of responders demonstrated dysanaptic lung growth suggesting relatively small airways compared to their lung size. A better understanding of how airways and lung parenchyma grow in BPD patients may shed light on disease progression.

Conflict of Interest Disclosures: The authors have no conflicts of interest relevant to this article to disclose.

Funding/Support: No specific support

Table 1. Demographics

	Responders (n = 59)	**Non-responders (n = 34)**	**p-value**
Gestational Age	25.7 (24.4 – 27.0)	25.3 (24.6 – 27.0)	0.90
Birth weight	698 (585 – 883)	724 (589 – 920)	0.53
PMA @ iPFT (weeks)	51 (45 – 57)	53 (47 – 70)	0.10
Post-partum age (mos) @iPFT	5.8 (4.7 – 10.3)	5.8 (4.4 – 7.5)	0.17
Weight @ iPFT	4.5 (3.7 – 5.4)	4.5 (3.7 – 6.7)	0.38
Growth Velocity (g/day)	10.5 (8.9 – 12.7)	9.3 (7.2 – 12.3)	0.07
Length @ iPFT	53 (49 – 57)	54 (50 – 62)	0.27
Length z-score @ iPFT	-2.11 (-3.05 – -1.18)	-1.80 (-3.81 – -1.00)	0.70
Respiratory support @iPFT			
Non-invasive	22 (37%)	17 (50%)	0.28
Endotracheal tube	20 (34%)	6 (18%)	0.15
Tracheostomy	17 (29%)	11 (32%)	0.82
Family history of asthma	23 (41%) (n = 56)	8 (27%) (n = 30)	0.24
Pregnancy tobacco exposure	20 (36%) (n = 56)	14 (42%) (n = 33)	0.65
Antenatal Steroids	48 (84%) (n = 57)	27 (79%) (n = 34)	0.58
Black	15 (25%)	11 (32%)	0.48
White	41 (69%)	19 (56%)	0.26
Severe IVH	4 (7%)	4 (12%)	0.46
PDA ligation	23 (41%)	14 (41%)	1.0
NEC	5 (8%)	1 (3%)	0.41
Grade 3 BPD	39 (66%)	19 (56%)	0.38
Grade 2 BPD	14 (24%)	10 (29%)	0.63
Grade 1 BPD	1 (2%)	1 (3%)	1.0
Unknown @ 36 wks	5 (8%)	4 (12%)	0.72
RSS @ 36 wks	6.2 (4.1 – 8.9) (n = 49)	7.5 (3.8 – 9.1) (n = 25)	0.59

Data shown as median (intraquartile range) or number (percent)
PMA, post-menstrual age; iPFT, infant pulmonary function test; Growth velocity from birth to iPFT using the exponential calculation; length Z-score calculated from CDC-NCHS length curves 0 – 36 months of age; IVH, intraventricular hemorrhage; PDA, patent ductus arteriousus; NEC, necrotizing enterocolitis; RSS, respiratory severity score

Table 2. Pre-bronchodilator iPFT Results

	Responders (n = 59)	Non-responders (n = 34)	p-value
PHENOTYPE			
Obstructive	34 (58%)	13 (38%)	0.087
Restrictive	2 (3%)	6 (18%)	**0.048**
Mixed	23 (39%)	15 (44%)	0.67
Moderate/Severe Obstruction	53 (93%)	18 (64%)	**0.002**
FLOWS			
FVC (% predicted)	76 (61 – 90)	77 (66 – 102)	0.41
$FEV_{0.5}$ (% predicted)	42 ± 13	55 ± 16	**<0.0001**
$FEV_{0.5}$/FVC (% predicted)	57 ± 18	70 ± 20	**<0.005**
FEF_{50} (% predicted)	13.2 (7.4 – 26.2)	28.4 (15.7 – 66.0)	**<0.001**
FEF_{25-75} (% predicted)	11.5 (7.2 – 21.7)	24.7 (13.0 – 56.0)	**<0.001**
VOLUMES			
FRC (% predicted)	112 (68 – 150)	97 (69 – 115)	0.14
RV (% predicted)	124 (72 – 171)	108 (76 – 125)	0.17
TLC (% predicted)	96 (82 – 120)	85 (73 – 121)	0.21
RV/TLC	54.5 (47.7 – 59.7)	47.7 (43.7 – 54.5)	**0.002**
FRC/TLC	65.1 ± 7.4	57.0 ± 9.5	**<0.0001**
VC (ml)	97 (74 – 138)	118 (93 – 154)	**0.035**
COMPLIANCE			
C_{RS} (% predicted)	64 (47 – 99)	74 (64 – 95)	0.20
C_{RS}/kg	1.00 (0.87 – 1.21)	1.08 (0.92 – 1.49)	0.30

Data shown as median (IQR) or number (percent)
FVC, forced vital capacity; $FEV_{0.5}$, forced expiratory volume in 0.5 seconds; FEF_{50}, forced expiratory flow at 50% of vital capacity; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; VC, vital capacity (TLC – RV)

Table 3. Logistic Regression Parameters

	OR	95% CI	p-value
$FEV_{0.5}$	0.93	0.88 – 0.99	**0.022**
$FEV_{0.5}$/FVC	1.01	0.97 – 1.07	0.53
FEF_{50}	0.93	0.82 – 1.07	0.30
FEF_{25-75}	1.06	0.92 – 1.22	0.41
RV/TLC	0.97	0.90 – 1.05	0.47
FRC/TLC	1.19	1.07 – 1.33	**0.001**
VC	0.99	0.98 – 1.01	0.46
DR	0.011	0.001 – 0.195	**0.002**

OR, odds ratio; 95% CI, 95% confidence intervals
Note values for DR have a relatively narrow range (0.013 – 0.856)

Table 4. Area under the receiver operating characteristics curve

	AUROC	**95% CI**
Pre-BD $FEV_{0.5}$	0.73	0.62 – 0.84
FRC/TLC	0.74	0.64 – 0.84
DR	0.68	0.56 – 0.79

AUROC, area under the receiver operating characteristics curve
95% CI, 95% confidence interval

Table 5. Outcomes

	Responders (n = 59)	**Non-responders (n = 34)**	**p-value**
Survived	54 (92%)	33 (97%)	0.41
Total ventilator days	168 (102 – 312)	141 (85 – 257)	0.36
Total ventilator days survivors	163 (99 – 268)	141 (83 – 237)	0.59
Ventilator days after iPFT	56 (22 – 146)	72 (32 – 261)	0.62
Length of stay (days)	316 (217 – 468)	294 (208 – 479)	0.58
Length of stay after iPFT (days)	139 (73 – 287)	97 (55 – 195)	0.13
Tracheostomy after iPFT	4 (7%)	1 (3%)	0.65
Discharge on IMV	6 (10%)	2 (6%)	0.71

iPFT, infant pulmonary function testing; IMV, invasive mechanical ventilation

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Figure 1.

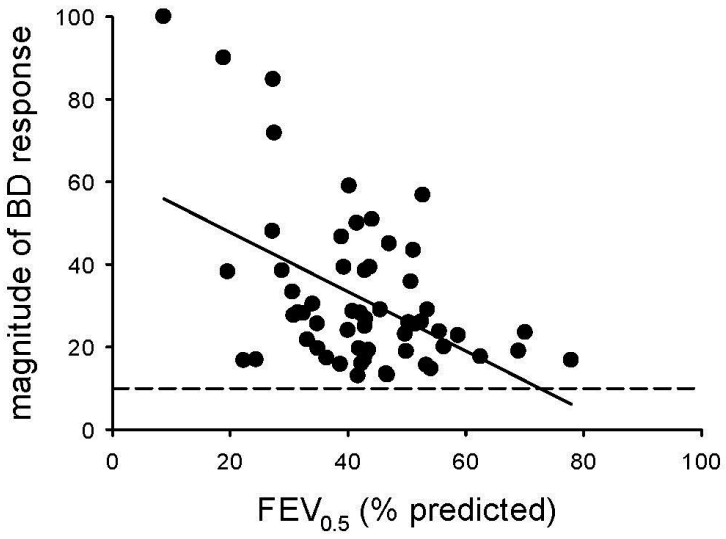

Figure 1. The magnitude of BDR is negatively correlated with $FEV_{0.5}$. The linear regression fit (solid line) ($y = -0.72x + 62$, $R = 0.49$, $R^2 = 0.24$, $p<0.001$) suggests that 24% of the variation in the magnitude of BDR is due to $FEV_{0.5}$. The dashed line represents the threshold for BDR.

Figure 2.

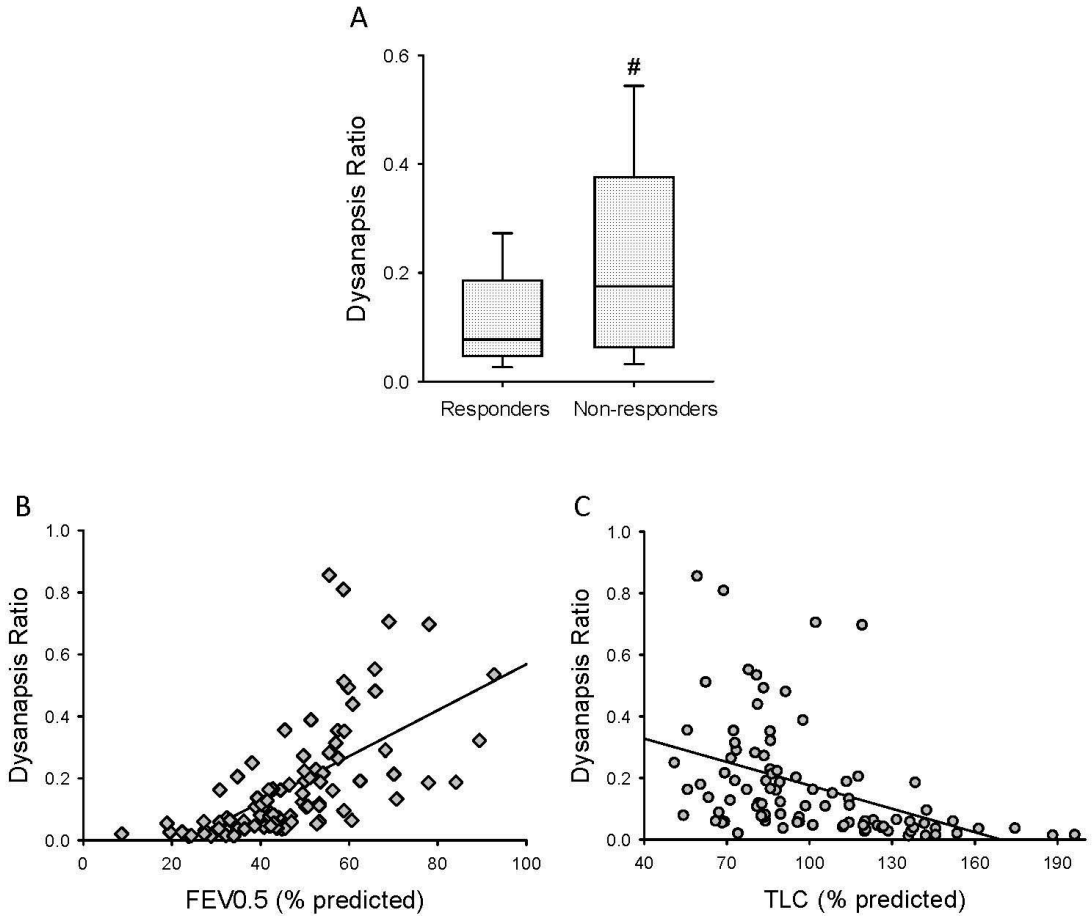

Figure 2. DR was significantly larger in non-responders than in responders (**A**). DR was correlated with the FEV0.5 (**B**) (linear regression fit; $y = 0.007x - 0.174$; $R = 0.62$; $R^2 = 0.39$; $p<0.001$). **C)** DR is negatively correlated with TLC ($y = -0.003x + 0.434$; $R = 0.44$; $R^2 = 0.19$; $p<0.001$).