



Original Research Article

Pulmonary function tests in preterm infants with bronchopulmonary dysplasia

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ABSTRACT

Introduction: BPD (bronchopulmonary dysplasia) is the most common complication of preterm birth for all gestational ages. The phenotype seen with BPD is the end result of a complex multifactorial process in which various pre-and postnatal factors compromise normal development in the immature lung. The aim of this study was to monitor the pulmonary function in preterm infants with bronchopulmonary dysplasia, and to declare the hypothesis that BPD has different phenotypes, that could be detected by iPFT during their initial NICU stay.

Materials and Methods: This is a prospective study, in the period from Feb 2015 till April 2018. It includes 32 preterm infants (gestational age <37 weeks), were diagnosed as having primary bronchopulmonary dysplasia (BPD). Pulmonary Function Test (PFT) was done for all patients one day before discharge from NICU.

Results: the median gestational age at birth was 29.6 weeks (IQR, 27.6-28.9) and the median birth weight was 1500 g (IQR, 945-1760). At the time of iPFT, the median postmenstrual age 44 weeks (IQR, 39-47), the median weight was 4.25 kg (IQR, 3.25-5.350). There were 19 patients (60%) with obstructive, 9 patients (29%) with mixed, 4 patients (11%) with restrictive phenotypes.

Conclusions: our findings reveal that BPD has 3 distinct phenotypes. The different phenotypes of BPD must be taken into consideration in the management of such patients for better outcome. Future researches are needed in a larger scale to define accurately the bronchopulmonary dysplasia phenotypes

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1. Introduction

Although advances in neonatal care in the past 20 years have decreased, the frequency of several morbidities associated with prematurity, an increased incidence of poor long-term pulmonary outcome is observed, due to, in part, increased survival of very low birth weight (VLBW) infants¹. Gas exchange in these tiny neonates must take place in developmentally fetal lungs, characterized by ongoing differentiation and growth. Survival usually requires comprehensive and invasive treatments including assisted ventilation and long periods of oxygen supplementation². Thus, preterm birth and the necessary respiratory support may disturb fine-tuned programmed patterns of fetal lung development, potentially with long-lasting negative effects

on lung function³.

Over the past few years, BPD (bronchopulmonary dysplasia) was the most common complication of preterm birth for all gestational ages (GAs) from 22 up to 28 weeks, overall affecting about 40% of infants born <28 weeks⁴. Criteria to define BPD have historically lacked uniformity. The earliest clinical definition of BPD was limited to oxygen requirement at 28 days with consistent radiologic changes⁵. The definition now takes into account total duration of oxygen supplementation, positive pressure requirement and gestational age, in addition to oxygen dependency at 36 weeks post menstrual age (PMA)⁶.

The phenotype seen with BPD is the end result of a complex multifactorial process in which various pre-and postnatal factors compromise normal development in the immature lung⁷. In addition to prematurity, several other

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factors can contribute to disruption of alveolar growth and pulmonary vascular development including but not limited to mechanical ventilation, oxygen toxicity, pre- and postnatal infection, inflammation, and growth restriction or nutritional deficits. Genetic predisposition is recognized to further modify the risk of the disease⁸.

The phenotype of BPD after early childhood is poorly described. There are no human biopsy studies and structural characteristics must be inferred from functional investigations. Airway obstruction has repeatedly been reported for children born preterm, and those with BPD generally do worse⁹. However, there are little pulmonary function data in the literature from infants with established sBPD during the initial NICU hospitalization.

The aim of this study was to monitor the pulmonary function in preterm infants with bronchopulmonary dysplasia, and to declare the hypothesis that BPD has different phenotypes, that could be detected by iPFT during their initial NICU stay.

2. Materials and Methods

This is a prospective study, was held in Prince Fahad Bin Sultan Hospital, Saudi Arabia, in the period from Feb 2015 till April 2018. It includes 32 preterm infants (gestational age <37 weeks), were diagnosed as having primary bronchopulmonary dysplasia (BPD). Pulmonary Function Test (PFT) was done for all patients one day before discharge from NICU, after being carefully assessed by pulmonology and NICU teams. Paternal consent was obtained from all patients prior to the study.

2.1. Criteria for diagnosis of BPD

For those born at gestational age (GA) < 32 weeks. BPD referred to requirement of oxygen support (>21%) for at least 28 days and a subsequent assessment at 36 weeks PMA or discharge, whichever comes first. In those born with GA > 32 weeks, BPD referred to the requirement of supplemental oxygen < 21% for at least 28 days and a subsequent assessment at 56 days post-natal or discharge, whichever comes first. At the time of this assessment, those infants with no oxygen requirement were classified as having mild BPD. Moderate BPD was diagnosed in those requiring <30% oxygen and severe BPD in those with a need for positive pressure ventilation/continuous positive pressure (PPV/CPAP) and /or oxygen requirement >30%¹⁰.

2.2. Pulmonary function tests

PFT was performed in the pulmonary function Unit of Prince Fahad hospital, by using Baby Body Plethysmograph (VIASYS Healthcare GmbH, Hochberg, Germany) with raised-volume rapid thoracic compression technique, to examine tidal breathing flow volume loop (TBFVL) and functional residual capacity (FRCp). Infants were sedated

with oral chloral hydrate (30-50 mg/kg) 30 min prior to assessment. After sedation, body weight and crown -heel length were measured before PFTs. For safety reasons the infant was monitored (pulse oximetry) throughout the measurement and tidal flow (volume) and pressure at the airway opening were displayed continuously on the monitor whenever mask and apparatus are connected. The main parameters of TBFVL were tidal volume (VT), respiratory rate (RR), ratio of inspiration to expiration time (Ti/Te), ratio of time to peak tidal expiratory flow to total expiratory time (TPTEF/TE) and peak tidal expiratory flow (PTEF). A minimum of five regular tidal breaths were taken to establish end-expiratory level before starting the balloon shutter to achieve a brief airway occlusion at end-inspiration. Between 5 to 10 occlusions were performed and mean of three to five valid measurements of FRCp were reported synchronously and up to three satisfactory measurements were obtained. After collecting pulmonary function data, patients were classified into 3 phenotypes obstructive, restrictive or mixed.

2.3. Data analysis

Data acquisition and analysis were performed on a Windows 98-based workstation (Jaeger Lab4 software-version 4.56). Online data sampling and reanalysis were based on the structural Jaeger Screen display. Results were displayed online instantaneously but could be subsequently checked for quality control, according to current ERS-ATS recommendations and as defined in the online supplement, before acceptance. Results were compared to standard references values of pulmonary function test parameters established by other authors in healthy infants.

2.4. Statistical analysis

Data were statistically described in terms of median (interquartile range [IQR]) or percentage unless otherwise specified. Comparison of numerical variables between the study groups was done using student t test for independent samples. Correlation between various variables was done using Pearson moment correlation equation for linear relation. P value less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft window.

3. Results

32 preterm infants with the primary diagnosis of BPD were included in the study. The demographic data of the entire study are given in table 1. In general, these patients were born preterm and 3 of them of extremely low birth weight (< 1000 g) and thus were at high risk for comorbidities of preterm delivery (Table 1). These patients had relatively

long initial stay NICU hospitalization (Table 1). The iPFT was done at a median PMA of 44 weeks or a median corrected chronological age of 8 weeks.

The iPFT data are presented in Table 2, according to these data patients were classified into 3 groups or phenotypes: (1) obstructive ($FEV_{0.5\%} < 80\%$ predicted and total lung capacity [TLC] $\geq 90\%$ predicted), (2) restrictive (TLC $< 90\%$ predicted and $FEV_{0.5\%}$ and/or forced vital capacity [FVC] $\geq 90\%$ predicted), (3) mixed (TLC $< 90\%$ predicted, and $FEV_{0.5\%}$ and/or FVC $< 90\%$ predicted). 60% of the patients (19 patient) has obstructive phenotype, followed by mixed phenotype 29% (9 patients), and restrictive phenotype is the least (only 4 patients). For the restrictive and mixed phenotypes, Crs was much lower than that of the obstructive group but not to the point to be statistically significant. Lung volumes were significantly lower in the restrictive and mixed types, compared to obstructive group.

How the difference among patients according to their phenotypes, there were no statistical differences among the three groups as regard sex, gestational age, birth weight, antenatal steroids, incidence of NEC, IVH and sepsis. For the use of noninvasive support the restrictive phenotype was significantly higher than the other 2 phenotypes, but there was no statistical difference between the three phenotypes as regard need for endotracheal intubation or tracheostomy. There was no statistical difference between the three groups in the number of ventilation days, and only 2 patient in the obstructive phenotype discharged on ventilator.

4. Discussion

Measurements of lung function with PFTs early in life can improve understanding of the determinants of lung growth and facilitate the evaluation of new therapeutic interventions and current clinical strategies¹¹. In this study, pulmonary function tests were done early for premature infants diagnosed with bronchopulmonary dysplasia, during their initial stay in NICU, the patients were classified into 3 distinct phenotypes according to their pulmonary function data, which were studied at a median age of 44 wks PMA, and this consistent with the hypothesis previously suggested by similar study of Edward et al, 2018, which stated that BPD diagnosed early during NICU admission has different phenotypes. Management and mechanical ventilation strategy can be changed according to the phenotype of bronchopulmonary dysplasia, thus improving the patient outcome.

In this study the majority of the patients have the obstructive phenotype (60%), in agreement with Beverly et al.¹², who stated that infants with a history of BPD have pulmonary function abnormalities in the form of mild to moderate airway obstruction and airway trapping. According to Korhonen et al.,¹³ Compared to term-born, children with BPD have a distinct pattern of

airway obstruction and inflammation. The airflow limitation experienced by BPD survivors is more often a fixed obstruction, likely due to a combination of irreversible, structural airway changes and neutrophilic inflammation¹⁴. A study done by Schmalisch et al¹⁵, included 386 VLBW (very low birth weight) infants who were diagnosed as severe neonatal lung disease defined in the study as needed mechanical ventilation, pulmonary function tests were significantly and independently associated with increased respiratory and airway resistances, reduced FRC (functional residual capacity), lower respiratory compliance. In a study done by Filippone et al.⁹, on 18 infants with a history of moderate to severe BPD, demonstrated severe reductions in FEF75, and air trapping as shown by increased RV/TLC values.

Very few studies demonstrated restrictive phenotype, in this study 4 patient's represent 11% of the study group, have pure restrictive phenotype. This can help determine the plan of management for patients with bronchopulmonary dysplasia, and change of the strategy of mechanical ventilation which depend on high tidal volume and slow rate for those patient with classical bronchopulmonary dysplasia with obstructive phenotypes, also patient can respond clinically to removal of positive high pressure¹⁶. It was observed that only one patient of the four with restrictive bronchopulmonary dysplasia needed invasive measurement with endotracheal intubation, compared to 12 patients in the obstructive group. Ventilator days were much less in the restrictive, no patient in the restrictive group needed ventilator on discharge, compared to the obstructive group in which 2 patients discharged on ventilator. This means that the type of respiratory support and its duration differ according to the phenotype of bronchopulmonary dysplasia.

In this study 9 patients (29%) have mixed phenotype, as they have decreased both TLC, and FEV and or/FVC $< 90\%$ predicted. 77% OF patients of this group needed intubation and mechanical ventilation, but improved faster and needed less ventilation days than the obstructive group. In a study done by Edward, et al about 40% of the patients (44 patients) had mixed obstructive and restrictive phenotypes, they had significant reduction in FEF50%-25-75%, FEV_{0.5}, FRC, TLC and RV, and also they had less ventilation days than needed by the other obstructive patients. This proves that strategy for mechanical ventilation and its duration, changes according to the phenotype of bronchopulmonary dysplasia.

A study done by Choukroun¹⁷ on 151 preterm babies with bronchopulmonary dysplasia, all the participants, showed significantly lower forced vital capacity (FVC), FEV₁, forced mid-expiratory flow (FEF₂₅₋₇₅), peak expiratory flow (PEF), vital capacity (VC), total lung capacity (TLC), functional residual capacity (FRC), and higher residual volume (RV) and RV/TLC values than predicted values. 11% of the patients had restrictive or

Table 1: Demographics of the entire study

	Median [IQR] OR % (n/N)
Gestational age, wk	29.6[27.6- 28.9]
Birth wt., g	1500[945- 1760]
SGA	9%(3/32)
Antenatal steroids	85% (27/32)
IVH	35%(11/32)
PDA	25% (8/32)
SEPSIS	55% (18/32)
Necrotizing enterocolitis	9.6 % (3/32)
Ventilator, d	27 [15-32]
Length of stay, d	48 [35-54]
Age at iPFT, wk. PMA	44 [39-47]
Weight at iPFT, g Length at iPFT, cm	4250 [3250-5350] 53 [48.4- 59.5]

SGA small for gestational age, IVH intraventricular hemorrhage, PDA patent ductus arteriosus.

Table 2: iPFT results by BPD phenotypes

	Entire study, Median [IQR] Or % (n/N)	Obstructive, Median [IQR] Or % (n/N)	Restrictive, Median [IQR] Or % (n/N)	Mixed, Median [IQR] Or % (n/N)	P
Crs, % predicted	12.3 [11-13.5]	14.3[10.8- 15.8]	11.4[9.8-11.6]	12[10.8- 13]	0.19
FVC, % predicted	74[60-91]	92[73-103]	57[60-71]	74[66-81]	<.001
FEV 0.5, % predicted	44[35-52]	41[33-51]	60[55-61]	46[43-57]	<0.001
FEV0.5 and/or FVC% predicted	59[45-71]	45[41-68]	91[89-94]	62[56-77]	<0.001
FEF25-75%, % predicted	14[13-34]	10[7-13]	66[53-74]	19[15-33]	<0.001
TLC, % predicted	87[73-110]	115[104-128]	74[64-76]	75[65-81]	<0.001
FRC, % predicted	96[73-138]	139[101-161]	67[51-94]	64[56-87]	<0.001
RV, % predicted	107[83-158]	157[117-183]	71[61-109]	69[52-94]	<0.001
FRC and/or TLC, % predicted	110[99-129]	121[103-141]	102[89-118]	103[93-119]	0.003
RV and/or TLC, % predicted	118[102-146]	136[123-159]	113[89-138]	105[92-117]	<0.001
Distribution of cases among study groups	–	60%(19/32)	11%(4/32)	29%(9/32)	–

Crs compliance, FVC forced vital capacity, FEF forced expiratory flow, FEV forced expiratory volume, FRC functional residual capacity, TLC total lung capacity, RV residual volume.

Table 3: Characteristics of patients according to their phenotypes.

	Obstructive, Median [IQR] or % (n/N)	Restrictive, Median [IQR] or % (n/N)	Mixed, Median [IQR] or % (n/N)	P
Sex				
Male,	61%(20/32)	49%(15/32)	59%(19/32)	0.23
Female	39%(12/32)	51%(17/32)	41%(13/32)	0.19
Gestational age, wk	29.4[27-30]	30[28-31]	28.9[27.7-30.4]	0.24
Birth wt, g	985[895-1345]	1015[950-1250]	956[875-1455]	0.03
SGA	12.8%(4/19)	25%(1/4)	22%(2/9)	0.19
Antenatal steroids	89%(17/19)	79%(3/4)	91%(8/9)	0.21
NICU Outcomes				
NEC	15.7%(3/19)	0% (0/4)	11.1%(1/9)	0.02
Grade 3 or 4 IVH	26%(5/19)	25%(1/4)	22%(2/9)	0.10
Sepsis	42%(8/19)	50%(2/4)	44.4%(4/9)	0.15
Noninvasive support	26%(5/19)	75%(3/4)	22.2%(2/9)	0.001
Endotracheal tube	74%(12/19)	25%(1/4)	77.8%(7/9)	0.030
Ventilator days	32[21-36]	19[23-31]	23[15-24]	0.13
Discharged on ventilator	10.5%(2/19)	0%(0/4)	0%(0/9)	0.04
Tracheostomy	10.5%(2/19)	0%(0/4)	0%(0/9)	0.04

SGA small for gestational age, NEC necrotizing enterocolitis, IVH intraventricular hemorrhage

mixed abnormalities.

There were no statistical differences between the three phenotypes as regard incidence of sepsis, NEC, IVH because these are related to the prematurity, more than to the lung condition. It is well known that infants with very low birth weight are at increased risk for both NEC and IVH¹⁸.

5. Conclusions

Patients with BPD were classified into three phenotypes according to their pulmonary function data: obstructive, restrictive and mixed type. The obstructive type was most predominant and associated with longer mechanical ventilation, and 10 % of this group needed ventilator on discharge. The restrictive type although few in number (only 4 patients), 75% of them needed non-invasive oxygen support, they had shorter ventilation days, and could be more easily weaned from mechanical ventilation. Determine the phenotype of bronchopulmonary dysplasia can help in the management of such patients, changing the mechanical ventilation strategy and thus improving their outcomes.

6. Limitation of the study

Larger number of patients in a higher center, are needed and can give more accurate results. Follow up pulmonary function for patients with bronchopulmonary dysplasia is needed, it can help detecting early deterioration of lung function and thus make early intervention possible.

7. Abbreviations

BPD-Bronchopulmonary Dysplasia, Crs-Compliance of the respiratory system, FEV0.5-Forced expiratory volume at 0.5 seconds, FVC-Forced vital capacity, iPFT-Infant pulmonary function testing, IQR-Interquartile range, PMA-Postmenstrual age, Rrs-Resistance of the respiratory system, SGA-Small for gestational age, TLC-Total lung capacity.

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9. Source of Funding

None.

10. Conflict of Interest

None.

References

- Day CL, Ryan RM. Bronchopulmonary dysplasia: new becomes old again! *Pediatr Res*. 2017;81(1-2):210–3.
- Coalson JJ. Pathology of Bronchopulmonary Dysplasia. *Semin Perinatol*. 2006;30(4):179–84.
- Fanaroff AA, Hack M, Walsh MC. The NICHD neonatal research network; 2003.
- Stoll BJ, Hansen NI, Bell EF. trends in care practices, morbidity, and mortality of extremely preterm neonates. *JAMA*. 1993;314:1039–51.
- Ibrahim J, Bhandari V. The definition of bronchopulmonary dysplasia: an evolving dilemma. *Pediatr Res*. 2018;84(5):586–8.
- Poindexter BB, Feng R, Schmidt B, Aschner JL, Ballard RA, Hamvas A, et al. Comparisons and Limitations of Current Definitions of Bronchopulmonary Dysplasia for the Prematurity and Respiratory Outcomes Program. *Ann Am Thoracic Soc*. 2015;12:1822–30.
- Collaco JM, McGrath-Morrow SA. Respiratory Phenotypes for Preterm Infants, Children, and Adults: Bronchopulmonary Dysplasia and More. *Ann Am Thorac Soc*. 2018;15(5):530–8.
- Baraldi E, Filippone M. Chronic Lung Disease after Premature Birth. *N Engl J Med*. 2007;357(19):413.
- Filippone M. Childhood course of lung function in survivors of bronchopulmonary dysplasia. *JAMA*. 2009;302(13):1418–20.
- JOBE A, BANCALARI E. Bronchopulmonary Dysplasia. *Am J Respir Crit Care Med*. 2001;163(7):1723–9.
- Mcevoy CT, Aschner ML. Pulmonary Function Tests in Bronchopulmonary Dysplasia: Why, What, and How. Updates on Neonatal Chronic Lung Disease.
- Robin B, Kim YJ, Huth J, Klocksieben J, Torres M, Tepper RS, et al. Pulmonary function in bronchopulmonary dysplasia. *Pediatr Pulmonol*. 2004;37(3):236–42.
- Korhonen PH, Suursalmi PH, Kopeli T, Nieminen R, Lehtimäki L, Luukkaala T, et al. Inflammatory activity at school age in very low birth weight bronchopulmonary dysplasia survivors. *Pediatr Pulmonol*. 2015;50(7):683–90.
- Caskey S, Gough A, Rowan S, Gillespie S, Clarke J, Riley M, et al. Structural and Functional Lung Impairment in Adult Survivors of Bronchopulmonary Dysplasia. *Ann Am Thorac Soc*. 2016;13:1262–70.
- Schmalisch G, Wilitzki S, Roehr CC, Proquitté H, Bühner C. Differential effects of immaturity and neonatal lung disease on the lung function of very low birth weight infants at 48-52 postconceptional weeks. *Pediatr Pulmonol*. 2013;48(12):1214–23.
- Abman SH, Collaco JM, Shepherd EG. Interdisciplinary care of children with severe bronchopulmonary dysplasia. *J Pediatr*. 2017;181:12–28.
- Choukroun ML, Feghali H, Vautrat S, Marquant F, Nacka F, Leroy V, et al. Pulmonary outcome and its correlates in school-aged children born with a gestational age \leq 32 weeks. *Respir Med*. 2013;107(12):1966–76.
- Jen HC, Graber JJ, Hill JL, Alaish SM, Voigt RW, Strauch ED, et al. Surgical necrotizing enterocolitis and intraventricular hemorrhage in premature infants below 1000 g. *J Pediatr Surg*. 2006;41(8):1425–30.

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