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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Research Article

Longitudinal Study of the Respiratory Function in Preterm Born Children: Comparison Between Subjects with and without Bronchopulmonary Dysplasia

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Received: October 25, 2016; **Published:** November 05, 2016

Abstract

The long-term changes of the respiratory function in patients with broncho-pulmonary dysplasia (BPD) are still largely unknown.

Aim: To study longitudinally the lung function of patients with BPD approaching the adulthood, compared with preterm born subjects without BPD (non-BPD).

Methods: 23 preterm born subjects with a gestational age of 23 ± 3 weeks and birth weight of 1296 ± 543 gr were studied and divided in two groups, one with BPD (n = 13) and one without BDP (n = 10) according to the Shennan definition and then reclassified following the definition NICHHD (n = 16 BPD and n = 7 non-BPD). Pulmonary function testing was performed at age of 9.2 ± 2.2 yr (T1) and 15.2 ± 2.3 yr (T2). The two groups were compared both at T1 and T2 and changes from T1 and T2 were assessed in both groups.

Results: The functional parameters of the non-BPD subjects were in the normal range at T1, except FEF25-75% that, however, showed a tendency towards the normality at T2. The BPD patients had mild airflow obstruction, mainly localized in the small airways, with marked air trapping at T1. A significant improvement of lung volumes and maximal expiratory flows was observed at T2. Conclusions: The presence of BPD was associated with an obstructive ventilatory defect at age 9, substantially involving the peripheral airways that still persisted at age 15, although with a lesser degree of severity.

Keywords: *Broncho-Pulmonary Dysplasia; Pulmonary Function Test; Lung Functional Decline; Airflow Obstruction; Bronchial Hyper-Responsiveness*

Introduction

Broncho-pulmonary dysplasia (BPD) is a chronic lung disease of infancy that may develop because of mechanical ventilation (MV) and high fraction oxygen inhalation needed for the treatment of acute respiratory distress (RDS) after birth in premature newborns [1].

Since the first description in 1967 [2] new mechanisms of lung injury have emerged in BPD, and the clinical and pathological characteristics of pulmonary involvement have changed.

During the pre-surfactant era BPD was often described in heavier (mean birth weight 2200 gr) and less premature (mean gestational age 34 weeks) infants, while now it is more commonly found in smaller and more premature newborns who initially have very mild or

no clinical signs of RDS [3]. The pathology is currently characterized by disruption of normal lung development ("new" BPD), rather than marked fibro-proliferative changes in the lung ("old" BPD), reflecting differences in the patients characteristics (gestational age and birth weight) and available treatments such as surfactant therapy, maternal steroid use, protective ventilatory strategies, aggressive management of patent ductus arteriosus, improved nutrition [4].

Actually, it is the result of a dynamic process involving injury, repair and maturation following complex interactions among different adverse stimuli including inflammation, hyperoxia, mechanical ventilation and infection on developing lung. Studies in animal models have demonstrated that the inflammatory pulmonary response is central in the development of BPD [5,6]. Recently, infections, inflammatory modulation, unbalance of defence systems (antioxidant, anti-protease, neutrophil apoptosis) and abnormal vascular development have been focused as cause of the abnormal lung growth in the extremely preterm infants [7,8].

Most attention, however, has been paid on the role of supplementary oxygen therapy and mechanical ventilation. Kennedy and coworkers analysing 184 subjects, 28 of these with BPD, reported a closer association between the FEV_1 reduction and the birth weight rather than the gestational age, showing, however, that the oxygen dependence beyond 3 weeks was associated to a progressive loss of FEV_1 of approximately of 3% for every more week of supplementation [9]. However, it is still unclear how much and how long either oxygen therapy or MV can affect the respiratory function in BPD subjects.

Despite changes in perinatal care and new insights in the development of BPD, such lung disease after premature birth remains a major clinical problem and it functional long-term consequences are not well defined.

The incidence of BPD in very low birth weight infants has been reported to vary from 15 to 50%; the differences relate to the proportions of very immature infants included in the populations studied and the definition of BPD that was adopted [4].

In fact, several criteria have been used to diagnose BPD, including oxygen dependency at either 28 days of age [10] or 36 weeks postmenstrual age [11] and the chest radiograph features. At the National Institute of Child Health and Human Development (NICHHD) sponsored workshop it was proposed that infants should be considered as affected by BPD if they had been oxygen dependent for > 28 days and subsequently, they were classified as suffering from mild, moderate or severe BPD, according to the respiratory support requirements at a later date [Table 1] [12].

Gestational Age	< 32 wk	> 32 wk
Mild BPD	Breathing room air at 36 wk PMA	Breathing room air 56 day PNA
Moderate BPD	Need for < 30% FiO2 at 36 wk PMA	Need for < 30% FiO2 at 56 day PNA
Severe BPD	Need for < 30% FiO2 and/or positive pressure at 36 wk PMA	Need for < 30% O2 and/or positive pressure at 56 day PNA

Table 1: *NICHHD: Definition of Bronchopulmonary Dysplasia.*

PMA: post mestrual age, PNA: post-natal age

(From A.H. Jobe and E. Bancalari NICHD/NHLBI/ORD workshop Summary
Bonchopulmonary dysplasia Am J Res Am J Resp Crit Care Med 163:1723-1729, 2001 - modified)

The aim of this study was to assess longitudinally the respiratory function in a group of BPD ex-preterm children as compared to a group of ex-preterm non-BDP children to see the differences with increasing age in the two groups approaching the adulthood. The secondary aim was to assess the effect of different definitions of BPD on lung function results.

Materials and Methods

Twenty-three subjects (11 female and 12 male) with a history of prematurity, treated at the Neonatal Intensive Care Unit of the Spedali

Civili of Brescia (Italy), were consecutively recruited. They were born between 1988 and 1996 at a gestational age of 28.6 ± 2.7 weeks, with a birth weight of 1296 ± 544 gr.

Thirteen subjects were labelled as affected by BPD at the discharge as pre-term infants with oxygen requirement at 36 weeks of post-menstrual age, according to the Shennan's definition [Table 2] [11].

	gest.age wk	birth weight gr	O2 day	MV day	T1 age yr	T2 age yr
mean	28	1191	28.40	6.80	8.6	14.6
SD	1.56	321.31	16.91	5.97	2.0	2.0
range	26 – 32	950 – 2050	0 - 56	0 - 19	6 - 13	12 - 19

Table 2A: *Shennan Definition – Non-BPD group (n 10 subjects).*

	gest.age wk	birth weight	O2	day MV	T1 age	T2 age
mean	29	1417	149.16	23.00	9.7	15.7
SD	3.49	683.11	155.01	12.57	2.3	2.3
range	26 - 35	830 - 2800	38 - 600	2 - 43	6 - 13	12 - 19

Table 2B: *Shennan Definition – BPD group (n 13 subjects).*

All subjects were studied in two occasions, at age of 9.2 ± 2.2 years (time 1; T1) and 15.2 ± 2.3 years (time 2; T2), respectively.

Lung function assessment was performed by measuring slow vital capacity (VC), inspiratory capacity (IC), forced expiratory volume (FEV_1), forced vital capacity (FVC), Tiffeneau index (FEV_1/VC%), mean forced expiratory flow between 25 and 75% of expired FVC (FEF25 - 75%), and lung volumes such as total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV) were obtained by body pletysmography.

Methacholine challenge tests were also performed, according to a doubling dose inhalation protocol, starting from a dose of 35 mcg and finished with a dose of 1470 mcg (cumulative). Dose-response curve was obtained to compute $PD_{20}FEV_1$ (20% fall of FEV_1 from base-line).

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Pulmonary function tests were made using Vmax 22 Pulmonary Function System with mass flow meter and Autobox 6200 (Sensor Medics, Yorba Linda, California). The methacholine challenge test was carried out by using a MB3 dosimeter (Markos-Mefar, Bovezzo, Italy). Respiratory technicians were blinded to clinical details of the subjects. The American Thoracic Society guidelines were adopted to perform the pulmonary function testing. The predicted values were those suggested by the ATS/ERS [13].

At time 2 (T2) the subjects underwent the measurement of exhaled NO (FeNO), not available at the time of the first evaluation. FeNO was measured at a flow of 50 ml/sec (NO chemiluminescence analyser ECOMEDICS CLD 77AM, Durten, CH).

As previously mentioned, to be compared the subjects were divided in two groups of 13 BPD and 10 non-BDP, according to the Shennan's definition of BPD; subsequently, they were re-divided in two different groups with 17 BPD and 6 non-BDP, by using the NICHHD definition of BPD, making the same comparisons (Table 3).

	Gest.Age W	Birth weight	O2	day MV	T1 age	T2 age
mean	28	1228	24	5	9.6	15.0
SD	2.10	417.59	14.57	5.65	1.7	1.7
range	27 - 32	950 - 2050	0 - 35	0 - 14	8 - 13	14 - 19

Table 3A: *NICHHD definition - non-BPD group (n = 6).*

	Gest.Age W	Birth weight	O2	day MV	T1 age	T2 age
mean	29	1347	132	18	9.0	15.0
SD	2.98	591.22	145.56	11.68	2.3	2.3
range	26 - 35	830 - 2800	28 - 600	2 - 43	6 - 13	12 - 19

Table 3B: *NICHHD definition - BPD group (n = 17).*

Statistical Methods

Results of the lung function testing were analysed as percentage of the predicted values. Comparisons between the BPD and non-BPD groups, both at time 1 and at time 2, were made using the Mann-Whitney test, and the Wilcoxon test was used to assess the differences between time 1 and time 2 within groups. A p level < 0.05 was retained as statistically significant. Data were expressed as mean ± SD.

Results

Both BPD and non-BDP groups had mean VC and IC within the normal limits, with no significant differences between them at time 1 and at time 2. In both groups, however, VC and IC showed a significant increase (as % predicted) between 9 and 15 years [Table 4 and 5].

Lung Function parameters	Time 1		Significance
	BPD, n: 13	Non-BPD, n: 10	
SVC, %pred.	88.3 (15.5)	86.5 (9,3)	p = 0.925
FVC, %pred.	90.1 (15.6)	87.2 (10,9)	p = 0.514
FEV1, %pred.	82.9 (19.2)	90.4 (13,6)	p = 0.576
FEV1/SVC, pred.	76.2 (8.0)	85.6 (10,2)	p = 0.005
FEF25-75, pred.	33.7 (13.0)	48.7 (12,6)	p = 0.011
IC, %pred.	81.2 (13.4)	78.3 (13,9)	p = 0.664
FRC, %pred.	115.2 (28.5)	97.6 (21,9)	p = 0.100
RV, %pred.	165.4 (56.7)	118.1 (33,9)	p = 0.047
TLC, %pred.	107.5 (15.4)	94.6 (12,4)	p = 0.047

Table 4A

Data are expressed as mean +SD

Lung Function parameters	Time 2		p
	BPD (n.13)	Non-BPD (n.10)	
SVC, %pred.	94.5 (17.6)	92.2 (12.6)	p = 1.000
FVC, %pred.	92.2 (17.3)	90.9 (13.3)	p = 0.828
FEV1, %pred.	82.2 (22.2)	91.0 (19.5)	p = 0.456
FEV1/SVC, %pred.	71.8 (10.7)	82.3 (10.0)	p = 0.037
FEF25-75, %pred.	48.5 (21.9)	66.1 (19.4)	p = 0.094
IC, %pred.	88.4 (20.5)	86.6(16.7)	p = 0.385
FRC, %pred.	107.5 (22.8)	94.6 (16.8)	p = 0.121
RV, %pred.	138.0 (44.9)	110.0 (18,7)	p = 0.077
TLC, %pred.	104.5 (12.3)	96.2 (9.8)	p = 0.067

Table 4B

Data are expressed as mean +SD

Table 4: *BPD group vs non-BPD group at time 1 and time 2 (according to Shennan definition).*

At time 1, FEV_1/VC ratio and $FEF_{25-75\%}$ were reduced (as % predicted) in both groups, reflecting the presence of mild airflow obstruction, but these parameters were significantly lower in ex-preterm children with BPD as compared to those who didn't have BPD [Table 4, Figure 1]. At time 2, while FEV1/VC ratio was lower because of a relatively larger increase of VC than FEV_1, the $FEF_{25-75\%}$ value improved substantially in the BPD subjects (as % predicted), still remaining below the normal limits and significantly lesser than that of the non-BPD subjects [Table 5, Figure 1].

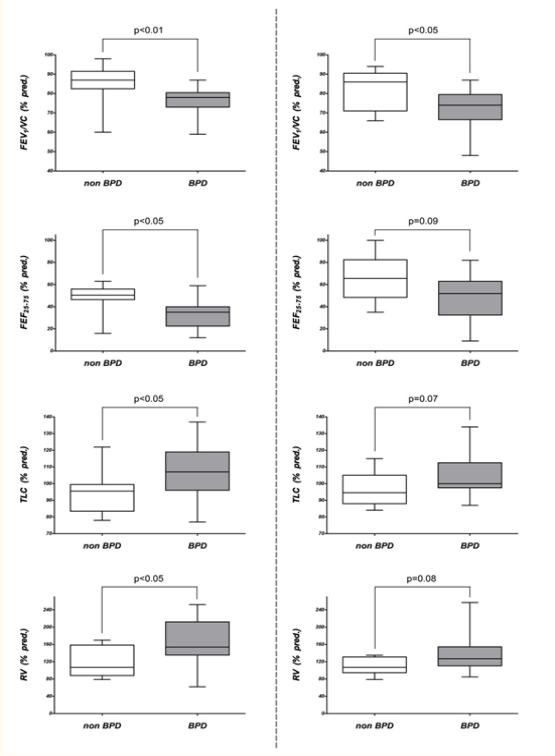

Figure1: *NonBPD vs BPD.*

Lung Function parameters	BPD		Significance
	Time 1	Time 2	
SVC, %pred.	88.3 (15.5)	94.5 (17,6)	p = 0.006
FVC, %pred.	90.1 (15.6)	92.2 (17.2)	p = 0.176
FEV1, %pred.	82.9 (19.2)	82.2 (22.2)	p = 0.769
FEV1/SVC, %pred.	76.2 (8.0)	71.8 (10.7)	p = 0.012
FEF25-75, %pred.	33.7 (13.0)	48.5 (21.9)	p = 0.004
IC, %pred.	81.2 (13.4)	88.4 (20.5)	p = 0.002
FRC, %pred.	115.2 (28.5)	107.5 (22.8)	p = 0.301
RV, %pred.	165.4 (56.7)	138.0 (44.9)	p = 0.057
TLC, %pred.	107.5 (15.4)	104.5 (12.3)	p = 0.791

Table 5A: *BPD group: time 1 vs time 2 (according to Shennan definition).*

Data are expressed as mean +SD

Lung Function parametrs	Non-BPD		Significance
	Time 1	Time 2	
SVC, %pred	86.5 (9.4)	92.2 (12.6)	p = 0.078
FVC, %pred.	87.2 (10,9)	90.9 (13.3)	p = 0.431
FEV1, %pred.	90.4 (13.6)	91.0 (19.5)	p = 0.921
FEV1/SVC, %pred.	85.6 (10.2)	82.3 (10.0)	p = 0.193
FEF25-75, %pred.	48.7 (12.6)	66.1 (19.4)	p = 0.009
IC, %pred.	78.3 (13.9)	86.6 (16.7)	p = 0.039
FRC, %pred.	97.6 (21.9)	94.6 (16.8)	p = 0.652
RV, %pred.	118.1 (33.9)	11.0 (18.7)	p = 0,652
TLC, %pred.	94.6 (12.4)	96.2 (9.8)	p = 0.625

Table 5B: *Non-BPD group: time 1 vs time 2 (according to Shennan definition).*

Data are expressed as mean +SD

At time 1, in the BPD group RV was abnormally increased, and RV and TLC were significantly higher than those of the non-BDP group, indicating a marked air trapping in the children with BPD.

At time 2, in the BPD group RV persisted above the normal limits, although significantly decreased (as % predicted) in comparison with time 1, and was still higher (p = 0.07) than that of the non-BPD subjects [Table 4 and 5, Figure 1].

At time 1, the ex-preterm children without BDP exhibited abnormal $FEF_{25-75\%}$ with a substantial improvement at time 2 (as % predicted), being all the other variables examined in the normal range.

At time 1, 6 (67%) of 9 (over 10) non-BDP subjects who performed the methacholine challenge test, were hyperresponsive (mean $PD_{20}FEV_1$ equal to 232 mcg), while at time 2, only 3 (33%) of 9 subjects did. The airway responsiveness of these subjects was significantly reduced at time 2 (mean $PD_{20}FEV_1$ changing from 127 to 797 mcg; $p < 0.05$).

At time 1, all the 8 (over 13) BPD subjects who underwent the methacholine challenge test (were hyper-responsive (100%) with a mean $PD_{20}FEV_1$ equal to 454 mcg. At time 2, one patient affected by a systemic illness had developed a mild bronchial obstruction, and only 2 of the other 7 patents tested with methacholine were hyper responsive (28%) with a reduction of mean PD_{20} FEV_1 from 323 to 889 mcg ($p < 0.04$).

The FeNO values were within the normal range of our lab. in both groups and were not different between them, amounting to 10.3 ± 10.7 and 9.1 ± 5.4 ppb for BPD and non-BPD subjects, respectively.

By using the NICHHD definition, we found differences nor at 9 years, neither at 15 years in the functional parameters between BPD and non-BDP groups.

Discussion

The results of this study show substantial differences in the respiratory function between BPD and non-BDP groups at the age of nine that, though less marked, persisted into adolescence.

The ex-preterm subjects had moderately reduced values of $FEF_{25-75\%}$ at the age of nine that in average reached the lower limits of the normal range at the age of fifteen. Conversely, the BPD ex-preterm subjects exhibited severe reduction of $FEF_{25-75\%}$ and marked increase of RV at the age of nine. Such airflow obstruction, characterized by initial normal values of FEV1 and FEV1/VC ratio in the presence of large air trapping, seems to be localized in the more peripheral airways. At the age of fifteen the BPD subjects, although showing a significant improvement of $FEF_{25-75\%}$ and RV (as % predicted), still had pathological airflow reduction and abnormal air trapping.

Mallory., *et al*. and Blayney., *et al*. already demonstrated that the pulmonary function improved over the time, even though these studies were conducted in much younger age and with much shorter interval of time, respectively [14,15].

Our data are partly consistent with those of Koumbourlis., *et al.* who studied 17 subjects with BPD between 8 and 15 years. These children had persistent reduction of $FEF_{25-75\%}$ in the adolescence, even if a concomitant, gradual normalization of air trapping was observed. Such airflow obstruction, however, was present only in some patients and was associated with airway hyper responsiveness [16]. In contrast with the results of Koumbourlis., *et al*. all our subjects with BPD had peripheral airway obstruction at time 1, and airway hyper responsiveness was present in all of them (8 over 13) who performed the methacholine test at time 1, but only in 2 of 7 subjects at time 2. We must say that Koumbourlis., *et al*. used a different definition of BPD for the inclusion of the subjects in the study and they had no control group.

Conversely, our findings support the results of Doyle., *et al*. who studied 147 subjects, 33 BPD and 114 ex-preterm subjects without BDP. In fact, at the age of eight they found an important reduction of maximal expiratory flows at low lung volumes suggesting the presence of small airways obstruction in the BPD subjects, and only a slight decrease of the maximal expiratory flow rates in the non-BDP subjects [17]. Although, in contrast with Doyle., *et al*. we found an abnormal increase in RV in the BPD subjects at the age of nine, the significant decrease of RV observed in the BPD subjects from time 1 to time 2 in association with the improvement of $FEF_{25-75\%}$, was consistent with the data reported by these Authors [18].

Both in BPD and in non-BPD subjects who underwent the methacholine challenge test, we found a significant reduction of bronchial hyper-responsiveness.

It is unclear whether airway hyper-responsiveness is caused by sustained lung injury in the neonatal period or if it is a manifestation of prematurity per se.

In fact, a similar prevalence of airway hyper-responsiveness has been demonstrated in children with history of premature birth, irrespective from RDS [19-21].

Many reference equations have been generated for spirometry in pediatrics, with variation in the generated ideal values. From this point of view the choice of the reference equations is critical to the diagnosis of lung disease. So we decided to compare three different reference equations: ERS+Zapletal [22,23], Hibbert and Hibbert '89 [24]. All the 3 reference equation sets detected significant differences between BPD and non-BPD subjects, but Hibbert '89 differed from the others, because giving lower normal values tends to underestimate the airflow obstruction.

The comparison of FeNO between BPD and subjects at the age of fifteen did not demonstrate significant differences. Our data are discordant with those of other studies that have reported a reduction of FeNO in BPD subjects [25,26]. Baraldi., *et al*. comparing 31 subjects with BPD at age 8.6 ± 0.3 years with 31 subjects born at term, found a reduction of FeNO levels measured at a 50 ml/sec flow in the BPD subjects. These FeNO values were significantly lower than those observed in 31 asthmatic subjects with similar degree of airway obstruction, suggesting a different site of airflow obstruction or a different pathogenesis of the functional defect [25].

The reclassification of the subjects according to the NICHHD definition caused the shift of subjects who were, according to the Shennan's definition, in the non-BPD group. By using the NICHHD definition we found no significant differences both at time 1 and time 2 in the lung functional parameters between BPD and non-BDP groups. Considering the small number of the subjects recruited, we did not stratify the BPD subjects in 3 groups of different severity, as the NCHHD definition does suggest.

Conclusion

Our results indicate that the occurrence of BPD in pre-term infants (according to the Shennan's definition) is associated with an obstructive ventilatory defect, mainly involving the peripheral airways, and a consequent substantial increase in RV in the childhood which is still present, although with a lesser degree of severity in the adolescence. These findings support the concept that BPD may represent a potential risk factor for developing COPD in adulthood.

Conflict of Interest

The authors deny any conflict of interest.

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Volume 2 Issue 4 November 2016