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Pulmonary sequelae in preschool children with BPD

Long-term effects of bronchopulmonary dysplasia on lung function: a pilot study in preschool children's cohort

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Abstract

Introduction: Although the long term negative effects of bronchopulmonary dysplasia (BPD) are well known, follow-up studies of preterm infants with BPD into childhood are lacking.

Methods: 42 pre-school children (age range 3-6 years) who were born before 32 weeks of gestational age and affected by BPD were enrolled. Pre-, peri-, and post-natal data were collected. During the follow up appointment complete physical examination and lung function (impulse oscillometry (IOS)) were recorded. The European Community Respiratory Health Survey (ECRHS) questionnaire was administered to all enrolled subjects.

Results: 30 patients were included in the final analysis. The BPD group did not differ in comparison to the non-BPD group in terms of lung function ($p>0.05$). By comparing all subjects enrolled, We detected extremely low-birth-weight (ELBW) infants with height-, weight-, and gender-related reference values and a significant trend of increasing resistance values ($R5_{Hz}$, $R5-20\ Hz$) and respiratory impedance ($Z5_{Hz}$) ($p<0.05$). No significant difference in bronchial reversibility test was observed among BPD non-BPD groups ($p<0.05$). The frequency of gastroesophageal reflux disease was significantly higher in patients with BPD when compared to non-BPD group ($p<0.05$). Significant differences in gestational age, oxygen supplementation (days), mechanical ventilation therapy (days), and sepsis between BPD and non-BPD groups were also observed ($p<0.05$). There were no significant differences in the prevalence of family and personal history of atopy and/or allergic diseases, tobacco exposure, respiratory symptoms, respiratory syncytial virus bronchiolitis, exercise induced dyspnea, treatment with β -2 bronchodilators and inhaled corticosteroids among the groups ($p>0.05$).

Conclusions: The respiratory function in pre-school children born with ELBW is characterized by an increase in impedance and resistance of small airways. No statistically significant differences were found between ELBW children with BPD and without BPD. With regards to the smallest gestational age, the longer duration of O_2 therapy during hospitalization, and sepsis significantly resulted in a worse respiratory function.

Key words: bronchopulmonary dysplasia; impulse oscillometry; long-term outcomes; prematurity; pre-school children.

1. Introduction

To date, bronchopulmonary dysplasia (BPD), (a chronic lung disease requiring oxygen supplementation (O₂) at 28 postnatal days or 36 weeks postmenstrual age and further classified as mild, moderate or severe based on the level of oxygen need at 36 weeks of gestation [1], is the major complication of premature birth with more than 8.000 newly diagnosed newborns annually in the USA [2].

The available therapies to prevent neonatal lung disease, including the antenatal steroids administration, surfactant, and ventilatory support permit the survival of infants but not without effects [3]. In this regard, observational clinical studies in BPD survivors suggest persisting anatomical and functional abnormalities. The adverse respiratory consequences are likely to be the result of a pulmonary injury related to inflammatory processes, compromised vascularization, and an impaired alveolarization process, contributing to the damage of the immature lung parenchyma and the small airways [4, 5].

Clinically, premature children also affected by BPD report a higher rate of respiratory illness, airway obstruction, and reactivity than those born at term without BPD [6].

However, the long-term consequences of BPD on children's respiratory health is still being studied.

We assume that both prematurity and BPD have a negative effect on the long-term respiratory disease as well as different neonatal factors, events, or treatments that play a role in the development or persistence of pulmonary changes in later life.

To test our theory, we investigated the impact of BPD severity on lung function in a cohort of pre-school children (age range, 3-6 years) who were born preterm, by performing impulse oscillometry (IOS). Furthermore, by using the European Community Respiratory Health Survey (ECRHS) questionnaire [7], we aimed to assess the respiratory health effects of BPD. And lastly, a potential relationship between demographic (age, gestational age (GA)); prenatal (history of maternal smoking during pregnancy, twins, intrauterine growth restriction (IUGR), treatment with corticosteroids (CS)); perinatal and neonatal (birth weight (BW), treatment with corticosteroids, instillation of surfactant, number of days on mechanical ventilation, oxygen supplementation, retinopathy of prematurity (ROP), persistent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), comorbidities (pneumothorax, diaphragmatic hernia, gastroesophageal reflux disease (GERD), pulmonary emphysema, respiratory distress syndrome (RDS), and septicemia)) data and BPD development was also investigated.

2. Methods

2.1 Participants

42 children (age range 3-6 years) born before 32 weeks of GA and BW <1500 gr were enrolled in the study. All children had been treated at the Neonatal Intensive care Unit (NICU) of Evangelico Villa Betania Hospital and Fate Bene Fratelli Hospital in Naples, Italy, between 2011 and 2014.

Inclusion criterium was a previous diagnosis of BPD, defined as the need for oxygen supplementation at 28 postnatal days or 36 weeks postmenstrual age. The severity of BPD was determined at 36 weeks GA as follows: 1) mild BPD - breathing air; 2) moderate BPD - need for oxygen supplementation <30%; 3) severe BPD - $\geq$ 30% oxygen supplementation and/or continuous positive airway pressure (CPAP) or mechanical ventilation [1].

Exclusion criteria included pulmonary, cardiac congenital malformations or any other pathological condition that did not allow a correct execution of the IOS technique.

Perinatal and neonatal data were obtained from medical records. Demographic and clinical data such as GA, BW, history of maternal smoking during pregnancy, twins, IUGR, treatment with prenatal and postnatal CS, instillation of surfactant, number of days on mechanical ventilation, oxygen supplementation, ROP, PDA, NEC, comorbidities (pneumothorax, diaphragmatic hernia, pulmonary emphysema, RDS), and sepsis, were collected.

All children underwent a medical examination. Demographic data and other clinical characteristics of the study subjects were collected using the European Community Respiratory Health Survey (ECRHS) questionnaire [7], containing validated questions on the: respiratory symptoms of the last 12 months; drug administration (bronchodilators, CS); tobacco exposure; family or personal history of asthma or eczema; a personal history of GERD, defined as reflux with pathologic consequences, such as esophagitis, nutritional compromise, or respiratory complications, requiring any kind of anti-reflux therapy [8]; respiratory tract infections; frequency of hospital admissions, also requiring ventilation or oxygen supplementation .

Child's length/weight was also taken. Pulmonary function was measured by IOS.

Ethical Committee from the Institutional Review Board approved the study. The parents' written informed consent was obtained.

2.2 Devices

Demographic data and other clinical characteristics of the study subjects were collected using questionnaires.

2.2.1 Impulse oscillometry (IOS)

The data retrieved from the IOS measurements represent complex functions of the lung such as small airway obstruction and airway mechanics, including the elastic properties of the lung [9, 10]. Testing was performed using the Jaeger MasterScreen-IOS system (Carefusion Technologies, San Diego, CA, USA). The method has been described in detail; [11, 12] in short, pressure impulses were sent from a loudspeaker through the respiratory system. The subjects were encouraged to breathe slowly (tidal breathing) with lips tightly sealed around the mouthpiece and supporting cheeks with their hands to avoid impulse pressure loss due to upper airway shunt. After quality inspection, the mean value of resistance at 5 and 20 Hz (R5; R20), the frequency dependence of resistance (R5–20) and the area of reactance (AX) were used for analysis [13, 14]. All children underwent bronchial reversibility test using nebulized albuterol (400 mcg) with the repetition of oscillometry after 15 minutes. The decrease in R5 by 30-35% was considered a positive bronchodilatory response [15, 16].

2.3 Data analysis

Data were statistically analyzed using the SPSS software (version 15.0) and presented as mean $\pm$ standard deviation (SD), or median and range for continuous variables, or numbers and percentages for categorical variables. Continuous variables were tested for normality distribution. Unpaired t-test was used to compare different groups for normally distributed variables. Due to non-normally distributed data, comparisons between independent groups were performed using the Mann-Whitney U test for continuous variables. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Patients characteristics

Of all 42 enrolled subjects, only 30 completed the study and the data was analyzed. 16 (38%) children were diagnosed with BPD ((19% mild (n=3/16); 69% moderate (n= 11/16); 12% severe (n= 2/16) (BPD group)) and 14 children were included in the control group (non-BPD group).

12 families withdrew their consent during the study. 25 children were lost to follow-up. 1 child was excluded due to a positive history of mental illness.

Demographic and perinatal data of the participants included in the final analysis are presented in Table 1.

Significant differences in GA, ventilation therapy (days), supplemental O₂ (days), treatment with postnatal CS, and septicaemia between BPD and non-BPD groups were observed (Table 1).

3.2 ECRHS questionnaire

Clinical data identified by ECRHS questionnaire is reported in table 2.

Among the enrolled patients, no significant differences in the prevalence/incidence of family and personal history of atopy and/or allergic disorders (asthma, eczema), and tobacco exposure were reported. Both groups showed normal ponderal and stature growth.

There were no significant differences in respiratory symptoms (dyspnea, cough, and wheezing) in the last 12 months between BPD and non-BPD groups ($p>0.05$).

44% (7/16) BPD and 21% (3/14) non-BPD patients reported persistent respiratory symptoms such as asthma (3 patients with moderate BPD and 2 non-BPD patients) and bronchitis (3 patients with mild BPD, 1 patient with moderate BPD, and 1 non-BPD patient).

The frequency of hospital admissions in the third year of life was significantly higher in patients with BPD when compared to non-BPD group (56% vs. 28%): n=5 admissions for non-respiratory syncytial virus (RSV) bronchiolitis; n=2 admissions for otorhinolaryngological diseases; n=1 admission for laryngospasm; n=1 admission for pneumonia; and n=1 admission for orchidopexy.

There were no significant differences in RSV bronchiolitis, exercise-induced dyspnea, treatment with β -2 bronchodilators and inhaled CS within the previous 12 months between groups.

The GERD rate was significantly higher in BPD group than non-BPD group ($p< 0.05$).

50% patients with BPD required a neuropsychological follow-up: n=2 patients reported psychomotor disorders and deafness; n=1 child was affected by deafness, and; n=5 children showed psychomotor disorders.

36% non-BPD group required a neuropsychological follow-up due to psychomotor disorders. Only one child reported deafness as well.

3.3 Impulse oscillometry (IOS)

The BPD group did not differ in comparison with non-BPD group ($p>0.05$; tab 3).

By comparing all enrolled extremely low-birth-weight (ELBW) infants with height-, weight-, and gender-related reference values [15, 16], a significant trend of increasing resistance values (R5Hz, R5-20 Hz) and respiratory impedance (Z5Hz) was detected (tables 4, 5).

Moreover, there were no significant differences in R5Hz, R5-20 Hz between BPD and non-BPD or within the different groups of BPD.

A positive bronchial reversibility test was observed in 44% (7/16) BPD vs. 36% (5/14) non-BPD group ($p>0.05$).

4. Discussion

Despite the fact that the negative long term effects of BPD are well known, follow-up studies of preterm infants with BPD into childhood are lacking. To fill this gap, our aim was to evaluate the influence of BPD severity on lung function assessed by IOS in a cohort of pre-school children with preterm births. In addition, by using the ECRHS questionnaire, we assessed the impact of pre-, peri-, and post-natal factors on respiratory health in childhood.

Regardless of BPD, our study showed an increase in respiratory impedance and resistance values of peripheral airways in all enrolled ELBW children compared to reference values. Specifically, the analysis of the oscillometry showed an increase in pulmonary resistance at 5 Hz, a difference in resistance between 5 Hz and 20 Hz and the respiratory impedance ($Z_{5\text{Hz}}$) in all enrolled ELBW children, suggesting that the abnormal respiratory pattern was reflecting an alteration in peripheral airway, typical of BPD. On the contrary and in contrast to the data available in the literature, no significant differences in the oscillometric parameters were found between children with BPD and those. This result could underline and confirm the weakness of the current definition of BPD which does not fully capture the mechanisms and risk factors for long-term pulmonary morbidity in premature infants. Many studies underline the lack of correlations between BPD and long-term pulmonary outcomes, probably due to differences in the definition of diagnosis among the various studies and the limited number of participants, as in our case. On the other hand, our results could suggest that the negative effect of prematurity on future health and respiratory function is still evident, despite progress in therapy. Evidence reported that although children with BPD are the most affected, even preterm children without BPD have a significant decrease in respiratory function. Regardless of the presence or absence of BPD, a postnatal lung injury is considered as contributor to the onset disease [21]. Respiratory function appears to be conditioned by early events to which the immature lung is exposed, and there is only a negligible recovery linked to the so-called “catch-up” pulmonary growth [22]. This would indicate the existence of a precocious and irreversible airway remodeling.

The mechanisms underlying the long-term respiratory effects in the pre-term population are still under debate. Inflammatory processes and altered vascularization, partly due to mechanical ventilation and oxygen supplementation, can contribute to irreversible damage of the immature pulmonary parenchyma and small airways [23, 24]. Histologically, in BPD, there is an alteration of the alveoli that appears more simplified and enlarged, probably due to a compromise of the process of postnatal alveolarization [25]. In post-mortem lung biopsies of newborns with histories of BPD, the transforming growth factor α (TGF- α) was increased. TGF- α is thought to damage the development of the airways and alveoli and inhibit pulmonary microvascular development, as reported in some animal models [26]. Also, the transforming growth factor $\beta 1$ (TGF- $\beta 1$) appears to be important in the development of BPD. In the bronchoalveolar lavage of children with BPD, Ichiba et al. [27] noted elevated TGF- $\beta 1$ levels compared to controls. TGF- $\beta 1$ suppresses the proliferation of alveolar epithelial cells, with consequent halting of alveolarization. This finding has also been shown in animal models [28]. In other studies, on post-mortem preterm newborns with severe BPD, Bhatt et al. found alteration of alveolar micro vessels as well as decreased serum vascular endothelial growth factor (VEGF) levels [29].

To track the respiratory health profile of enrolled ELBW children, the modified ERCHS questionnaire was submitted to the children's parents. When compared to children without BPD, children with BPD reported a higher incidence of GERD and, consequently, a more frequent use of drugs for treating GERD. This data correlates well with scientific evidence that reports how GERD, in addition to swallowing dysfunction and poor diet, is a factor contributing to the development of chronic lung injury [8, 17, 18]. Other important risk factors associated with the development of BPD appeared to be a lower gestational age, duration of the administration of oxygen supplementation, invasive mechanical ventilation, and sepsis. Supporting our findings, literature data reported that among infants with BPD, 95% have a very low birth weight (VLBW) [30]. Accordingly, due to the abnormal respiratory patterns, premature infants often require an increase in oxygen supplementation and mechanical ventilation that can further favour BPD onset. Lung injury from mechanical ventilation is due to volutrauma, barotrauma, and atelectrauma; when lungs are exposed to high tidal volumes, over distension causes release of pro-inflammatory cytokines, reduced expression of anti-inflammatory cytokines, and a stretch injury resulting in over-distending partially collapsed lungs [31]. Early studies performed in chronically ventilated preterm *vivo* model of BPD showed evidence both of non-uniform inflation patterns and impaired alveolar formation with an abnormal release of pro-inflammatory cytokines and elastin [31, 32]. Another pioneer study suggested that peak inspiratory ventilator pressure and requirement for assisted ventilation on day 4 of life are early predictors of BPD [33].

Sepsis is also a risk factor associated both with pulmonary deterioration resulting in BPD and prolonged hospital stay [31]. In the BPD group, more than 50% of children required hospitalization for respiratory diseases in the first 3 years of life, as reported in the literature [19, 20]. Since their immune defenses are not fully developed, preterm infants are more susceptible to systemic or localized infections. The subsequent inflammation from sepsis probably causes an increased neutrophil accumulation, a decreased lung alveolarization, and vascularization predisposing to BPD [31].

No significant differences were recorded regarding the potential relationship between demographic (age); prenatal (history of maternal smoking during pregnancy, twins, intrauterine growth restriction (IUGR), treatment with corticosteroids; perinatal and neonatal (treatment with corticosteroids, instillation of surfactant, ROP, PDA, NEC, comorbidities (pneumothorax, diaphragmatic hernia, pulmonary emphysema, and RDS)) data and BPD development. In this regard, our data is reflecting the controversial findings available in literature [31]. We cannot exclude that the lack of significance can be due to the small number of children examined as well as the lack of a comparison with a healthy control group.

Consequently, the limitations of this study concern the small sample examined and the lack of a healthy control group of at-term babies. For these reasons, some of the results may lack statistical significance, and therefore they may differ from other studies in the literature. Moreover, it was not possible to conduct a stratification by disease severity that could provide important feedback. Furthermore, a single evaluation from birth to the time of enrollment could be insufficient to stage lung damage, and, for this reason, we are planning a further follow-up study.

On the other hand, our study shows several strengths. One of the strengths of this study is the definition of BPD considered, which is more significantly related to long-term and lung pulmonary outcomes [34]. This study also investigated respiratory function in the pre-school-aged children (3-6 years) which has been rarely analyzed by the scientific studies available in the literature due to the difficult collaboration of these patients. The respiratory function data on age-related changes are very useful, allowing us to define the starting point and then tracing the progress of lung function over time.

5. Conclusions

Premature children with BPD reported higher rates of respiratory illness, airway obstruction, and reactivity compared to those born at term without BPD [6]. Currently, follow-up studies of preterm infants with BPD into childhood are lacking, especially because new developments in the care of premature infants have resulted in important changes in the clinical picture of BPD. Nevertheless, we strongly believe that by improving the current state of knowledge of long-term respiratory morbidity for infants with BPD remains a priority. To achieve this goal, we enrolled premature children with BPD and, *via* evaluated IOS, we evaluated their lung function. Moreover, we investigated the potential impact of pre-, peri- and post-natal factors on respiratory function. Our analysis revealed that prematurity, regardless of the development of BPD, affects the respiratory function in childhood as assessed by an increase in impedance and resistance of small airways recorded through IOS. Among pre-, peri- and post-natal factors, the small gestational age, a longer duration of oxygen therapy, and sepsis were resulting in a worse respiratory function in preschool-aged children.

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Conflict of interest

The authors have no conflicts of interest to disclose that could be perceived as prejudicing the impartiality of the research reported.

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Table 1. Demographic and clinical data of enrolled population.

	BPD* group (n=16)	Not BPD group (n=14)	P_{value}
Gender (M:F)*	9:7	6:8	0.46
Age (months)	71.43 ± 3.42	72.35 ± 1.59	0.56
Height (cm)	111.96 ± 2.22	113.32 ± 1.82	0.60
Weight (Kg)	19.55 ± 1.17	20.76 ± 1.09	0.33
BMI (Kg/m²)	15.41 ± 0.45	16.23 ± 0.67	0.32
GA (weeks)	26.38 ± 0.49	27.86 ± 0.49	0.04
BW (Kg)	0.88 ± 0.06	1.04 ± 0.70	0.13
IUGR (%)	5 (31.2%)	2 (14.2%)	0.26
Tobacco exposure during pregnancy (%)	0 (0%)	2 (14.3%)	0.48
Prenatal treatment with CS (%)	10 (62.5%)	6 (42.8%)	0.28
Treatment with surfactant (%)	14 (87.5%)	8 (57.1%)	0.06
Ventilation (days)	19.5 ± 5.08	4.9 ± 1.2	0.01
CPAP (days)	23.81 ± 3.31	13.14 ± 2.03	0.02
O₂ supplementation (days)	72.31 ± 3.88	32.64 ± 4.04	<0.0001
Postnatal treatment with CS (%)	7 (43.7%)	0 (0%)	0.007
PDA	7 (43.7%)	3 (21.4%)	0.14
Septicemia (%)	10 (62.5%)	5 (35.7%)	0.04
NEC (%)	2 (12.5%)	0 (0%)	0.49
Hemorrhagia intraventricular	2 (12.5%)	0 (0%)	0.49

*BPD: bronchodysplasia; M: male; F: female; cm: centimeter; Kg: kilograms; m: meter; GA: gestational age; BW: birth weight; CS: corticosteroids; CPAP: Continuous Positive Airway Pressure; O₂: oxygen; PDA: perviety ductus arteriosus; NEC: Necrotizing Enterocolitis.

Table 2. Clinical data identified by European Community Respiratory Health Survey (ECRHS) questionnaire.

	BPD* group (n=16)	Not BPD group (n=14)	P_{value}
Dyspnea (yes %)	6 (37%)	3 (21%)	0.26
Not infection-induced wheezing (yes %)	3 (19%)	3 (21%)	0.99
Cough (yes %)	8 (50%)	6 (43%)	0.73
Respiratory diseases requiring treatment (yes %)	7 (44%)	3 (21%)	0.26
Allergic diseases (yes %)	4 (25%)	2 (14%)	0.66
Atopic eczema (yes %)	4 (25%)	2 (14%)	0.66
Hospitalization during the first 3 years of life (yes %)	9 (56%)	4 (28%)	0.28
Hospitalization due to RSV* bronchiolitis (yes %)	1 (6%)	2 (14.2%)	0.59
Dyspnea induced by exercise (yes %)	4 (25%)	4 (28%)	0.99
Use of β-blockers during the last 12 months (yes %)	5 (31%)	4 (28%)	0.99
Use of CS* during the last 12 months (yes%)	7 (44%)	8 (57.1%)	0.28
Diagnosis of GERD* (yes %)	9 (56%)	2 (14%)	0.02
Use of drugs for GERD (yes %)	9 (56%)	2 (14%)	0.02
Normal ponderal and statural growth (yes %)	13 (81%)	13 (93%)	0.99
Tobacco exposure (yes %)	7 (44%)	8 (57%)	0.28
Psychomotor development follow up (yes %)	8 (50%)	5 (36%)	0.48

*RSV: respiratory syncytial virus; CS: corticosteroids; GERD: gastroesophageal reflux disease.

Table 3. Impulse oscillometry (IOS) values both in bronchopulmonary dysplasia (BPD) and not-BPD group.

	BPD* group (n=16)	Not BPD group (n=14)	P _{value}
Diff R5-R20	0.39 ± 0.05	0.30 ± 0.03	0.27
Z5Hz	1.14 ± 0.09	1.16 ± 0.06	0.94
R5Hz	1.09 ± 0.09	1.14 ± 0.06	0.86
R5Hz%	122.4 ± 9.7	136.6 ± 9.05	0.55
R20Hz	0.70 ± 0.04	0.83 ± 0.04	0.07
R20Hz%	97.5 ± 6.4	119.43 ± 6.4	0.05
X5Hz	0.30 ± 0.04	-1.51 ± 1.26	0.62
X5Hz%	105.5 ± 14.6	88.52 ± 8.6	0.29
Fres	21 ± 1.98	20.85 ± 2.11	0.67
AX	3.2 ± 0.55	2.45 ± 0.38	0.37
Δ Diff R5-R20 %	43.55 ± 26.6	29.9 ± 9	0.22
Δ Z5Hz %	18.31 ± 6.9	17.27 ± 4.9	0.56
Δ R5Hz %	17.51 ± 6.9	16.05 ± 4.9	0.53
Δ R20Hz %	3.5 ± 33	10.5 ± 17.2	0.95
Δ X5Hz %	7.4 ± 19.5	21.8 ± 9.2	0.59
Δ Fres %	-11.2 ± 26.4	-11.2 ± 26.4	0.15
Δ AX %	58.4 ± 7.8	27.26 ± 7.77	0.31

*BPD: bronchopulmonary dysplasia.

Table 4. Comparison of impulse oscillometry (IOS) values among extremely low-birth-weight (ELBW) infants and height-, weight-, gender-related reference values.

	ELBW* group (n=30)	Ref. values	P _{value}
R5Hz	1.11 ± 0.31	0.89 ± 0.09	0.0002
R20Hz	0.76 ± 0.03	0.71 ± 0.01	0.17
R5-R20Hz	0.33 ± 0.03	0.18 ± 0.002	0.0003
X5Hz	-0.27 ± 0.15	-0.28 ± 0.005	0.59
Z5Hz	1.15 ± 0.32	0.94 ± 0.01	0.0006

*ELBW: extremely low-birth-weight; Ref: reference.

Table 5. Comparison of impulse oscillometry (IOS) values among bronchopulmonary dysplasia (BPD) infants and height-, weight-, and gender-related reference values for BPD and among not BPD infants and height-, weight-, and gender-related reference values.

	BPD* group (n=16)	Ref. values BPD	Not BPD group (n=16)	Ref. values control	P_{value}	
R5Hz	1.09±0.09	0.90±0.02	1.14±0.06	0.88±0.01	0.03	0.003
R20Hz	0.70±0.04	0.72±0.02	0.83±0.04	0.70±0.01	0.82	0.02
R5-R20Hz	0.39±0.01	0.18±0.002	0.30±0.03	0.17±0.002	0.009	0.01
X5Hz	0.30±0.04	-0.28±0.007	-0.24±0.02	-0.28±0.005	0.47	0.16
Z5Hz	1.14±0.09	0.95±0.03	1.1±0.06	0.92±0.02	0.05	0.006

*BPD: bronchopulmonary dysplasia; Ref: reference.