


# Bronchopulmonary Dysplasia in Preterm Infants Born at Less Than 32 Weeks Gestation

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Yan-Ping Xu, PhD<sup>1</sup>

## Abstract

**Objectives:** Bronchopulmonary dysplasia (BPD) is a chronic pulmonary disorder affecting preterm infants. We studied the factors and echocardiographic evidence of early pulmonary hypertension (PH) associated with moderate or severe BPD. **Methods:** We retrospectively reviewed preterm infants who were born at <32 weeks gestation and admitted to the neonatal intensive care unit at the Children's Hospital of Zhejiang University School of Medicine between July 2013 and July 2015. **Results:** Forty-two preterm infants were enrolled in the study. All the patients received oxygen treatment for a mean of  $62.5 \pm 28.0$  days. The grades of BPD were classified as follows: severe, 35.7%; moderate, 40.5%; and mild, 23.8%. The time of ventilator and oxygen supplementation was longer in infants who developed PH. Severe BPD was related to PH at 28 days. **Conclusions:** These findings support the notion that early pulmonary vascular disease and long-term infection in preterm infants contributes to increased susceptibility for severe BPD.

## Keywords

bronchopulmonary dysplasia, prematurity

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## Introduction

Preterm infants <32 weeks gestation are now surviving in increased numbers.<sup>1</sup> Bronchopulmonary dysplasia (BPD) is a chronic pulmonary disorder affecting preterm infants. The “new” BPD differs from the BPD first described in 1967 by Northway et al.<sup>2</sup> Rather than fibrosis and scarring of the lungs, the new BPD is characterized by alveolar simplification and pulmonary vascular hypoplasia or dysplasia.<sup>3,4</sup> Long-term morbidities continue to be observed in preterm survivors. A number of studies have focused on identifying the risk factors for BPD. The influencing factors for BPD grade include mechanical ventilation, oxygen toxicity, inflammation, and other stimuli found in the neonatal intensive care unit (NICU) setting; however, preterm infants without such risk factors can still develop BPD. Indeed, there is a complex crosstalk between pulmonary alveolar and vascular development.

The role of factors for BPD grade and early-onset pulmonary hypertension (PH) among infants <32 weeks gestation remain unclear. We conducted a retrospective, single-center cohort study to determine the association

between influencing factors and mild/moderate/severe BPD. We hypothesized that echocardiographic evidence of early PH (PH between 7 and 28 days of life) is associated with moderate or severe BPD. Earlier detection may allow earlier intervention, which could minimize the progression of BPD and pulmonary vascular remodeling in the neonatal period.

## Subjects and Methods

We retrospectively reviewed the medical records of preterm infants who were born at <32 weeks gestation and admitted to the NICU at the Children's Hospital of Zhejiang University School of Medicine between July 2013 and July 2015. The Ethics Committee of the Children's Hospital of Zhejiang University School of

<sup>1</sup>The Children's Hospital of Zhejiang University School of Medicine, Hangzhou, China

### Corresponding Author:

Yan-Ping Xu, The Children's Hospital of Zhejiang University School of Medicine, Hangzhou 310052, China.  
Email: xuyanping726@hotmail.com



**Table 1.** Characteristics of Patients.

	Number	%	Median (Range) <sup>a</sup>
Gender	42		
Male	31	73.8	
Female	11	26.2	
Gestational age at birth (weeks)			28 (26-32)
Birth weight (g)			1147 (750-1800)
Small for gestational age	6	14.3	
Apgar score 1			6.2±2.1
Apgar score 5			7.4±1.9
Singler	25	59.5	
Multiplet	11	26.2	
In vitro fertilization and embryo transfer	6	14.3	
Respiratory distress syndrome	33	78.6	
Bronchopulmonary dysplasia	42		
Mild	10	23.8	
Moderate	17	40.5	
Severe	15	35.7	
Patent ductus arteriosus	17	40.5	
Surgical treatment	7	16.7	

<sup>a</sup>Data are presented as median (range) or mean±SD.

Medicine approved the study. A written informed consent for participation in the study was obtained from the parent of infants.

During the study period, 42 preterm infants were diagnosed with BPD. BPD was diagnosed if an infant received supplemental oxygen for  $\geq 28$  days. BPD was classified into mild, moderate, or severe forms at 36 weeks' postmenstrual age, as described by Jobe and Bancalari<sup>5</sup> as follows: mild BPD, breathing room air; moderate BPD, requiring oxygen supplementation ( $\text{FiO}_2$  of  $< 0.3$ ); and severe BPD, requiring  $\text{FiO}_2$  of  $\geq 0.3$  or positive pressure ventilation at 36 weeks gestation. We excluded infants with congenital heart disease (except patent ductus arteriosus [PDA], small ventricular septal defect, atrial septal defect, or patent foramen ovale), congenital diaphragmatic hernias, and the typical persistent PH of the newborn.

All study echocardiograms were performed by a pediatric echocardiography technician. The diagnosis of PH was made by echocardiography based on the following criteria: (1) velocity of tricuspid valve regurgitation  $\geq 3\text{m/s}$  in the absence of pulmonary stenosis or (2) flat or left-deviated interventricular septal configuration and right ventricular hypertrophy with chamber dilation.<sup>6,7</sup> Small-for-gestational age was defined as a birth weight less than the 10th percentile for gestational age.

## Statistical Analysis

Repeated cases have been excluded. Data for infant characteristics were expressed as the median and range

or mean  $\pm$  standard deviation or percentage. Enumeration data were analyzed by  $\chi^2$  test (Fischer's exact probability test). Measurement data were analyzed by variance analysis. We used the classification of BPD as the dependent variable, and all factors with significant associations emerging from the univariate analysis as independent variables. In all analysis,  $P < .05$  was considered significant. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS), Version 13.

## Results

Forty-two preterm infants were enrolled in the study, with 31 male (73.8%) and 11 female (26.2%) participants. The gestational ages ranged between 26 and 32 weeks (median = 28 weeks). The birth weight was 750 to 1800 g. All the infants received treatment in the NICU, with a mean hospital stay of  $78.8 \pm 29.9$  days. Thirty-one infants were on a ventilator after birth between 1 and 135 days. All the infants received oxygen treatment for a mean of  $62.5 \pm 28.0$  days. The BPD grades were classified as follows: severe, 35.7%; moderate, 40.5%; and mild, 23.8%. Thirty-three (78.6%) infants had respiratory distress syndrome at birth, and 7 (16.7%) infants had surgical management for PDA. The characteristics of the infants' studies are presented in Table 1.

The clinical characteristics of the study infants are presented in Table 2. The following previously reported risk factors for BPD were not statistically associated

**Table 2.** Comparison Between BPD Patients.

	BPD		
	Mild	Moderate	Severe
Gestational age at birth (weeks)	28.40±1.27	28.24±1.75	27.20±1.27
Birth weight (g)	1240.00±248.06	1172.35±282.04	1057.67±249.96
SGA	2/10	0/17	2/15
Resuscitation at birth (%)	2/10	9/17	5/15
Apgar score at 5 minutes	7.60±2.07	7.25±1.66	7.36±2.34
Male (%)	9/10	12/17	9/15
Age of mother (years)	30.80±5.05	28.83±5.18	31.83±5.67
Chorioamnionitis (Uu)	3/10	7/17	5/15
RDS (%)	7/10	14/17	12/15
NEC (%)	0/10	2/17	1/15
IVH (%)	1/10	4/17	1/15
PDA (%)	2/10	5/17	10/15*:#
ROP (%)	2/10	8/17	6/15
Surgical closure of PDA	1/10	1/17	5/15
Duration of O <sub>2</sub> use (days)	39.70±15.22	60.75±25.98*	79.53±26.24*:#
Duration of ventilator (days)	4.90±8.65	8.88±12.01	26.00±19.10*:#
Dexamethasone for BPD (%)	2/10	1/17	5/15
Duration of antibiotics (days)	25.60±10.86	23.88±10.49	46.50±27.14*:#
Caffeine use	3/10	6/17	4/15
Surfactant	6/10	9/17	11/15
PH 7 days	1/9	3/14	1/14
PH 14 days	0/10	1/16	2/13
PH 28 days	0/10	0/17	5/10*:#
PH 56 days	0/10	0/17	2/13
Age of discharge (days)	56.10±13.06	76.82±23.34	96.27±34.43*:#
Discharge body weight (kg)	2.61±0.51	3.08±0.72	3.46±0.73*

Abbreviations: BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome; PDA, patent ductus arteriosus; PH, pulmonary hypertension. SGA, small for gestational age; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity

\* $P < .05$  moderate or severe compared with mild. # $P < .05$  severe compared with moderate.

with severity in our study: gestational age, birth weight, gender distribution, chorioamnionitis, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity, and dexamethasone use for BPD. Severe BPD was more prevalent in infants with a long hospital stay after birth, duration of ventilator and oxygen use, PDA, and the duration of antibiotics use. The duration of ventilator and oxygen supplementation was longer in the PH infants. Severe BPD was related to PH at 28 days.

## Discussion

BPD is a chronic lung disease associated with prematurity and still lacks effective prevention and treatment.<sup>8-10</sup> The etiology and pathogenesis of BPD are still unclear. Some authors believe that the occurrence and development of BPD are associated with premature birth, inhalation of high concentrations of oxygen, a long duration

of mechanical ventilation, and infection.<sup>11</sup> Immature lung development at an early gestational age and low-birth-weight infants are the most basic factors for the occurrence of BPD; however, our study showed that there was no significant difference between the severity of BPD and gestational age/birth weight.

The relationship between chorioamnionitis and BPD is still controversial. One study demonstrated that exposure to histologic chorioamnionitis with/without funisitis and prolonged mechanical ventilation increase the risk for BPD,<sup>12</sup> while another study suggested that funisitis is protective for BPD.<sup>13</sup> Several studies have unveiled an association between elevated concentrations of pro-inflammatory cytokines in the amniotic fluid and the development of BPD.<sup>14</sup> Recently, it was reported that the difference between the incidence of BPD in preterm infants born from pregnancies complicated by chorioamnionitis and the control group was not significant.<sup>15</sup> Similar to other

investigators, we found that BPD severity is not associated with chorioamnionitis, unlike nosocomial infections. Most infections during the hospital stay are due to drug-resistant bacteria. Fetal pulmonary infection can inactivate surfactant and make the lung more susceptible to further injury from oxygen toxicity or mechanical ventilation, thus eventually leading to more severe BPD.

Our study showed that there is a relationship between PDA and BPD severity. PDA can significantly increase blood circulation in lung tissue, the probability of edema, and infection of lung tissue. PDA and BPD may have a cause-and-effect relationship. Several studies have reported an association between PDA and BPD.<sup>16-18</sup> The presence of increased left-to-right flow through a PDA could affect the assessment of PH by echocardiogram, but also could lead to pulmonary vascular remodeling and pulmonary vascular disease. Although PDA treatment is not directly associated with BPD, in our study, the impact could be encompassed by the association of early PH with BPD. Using a broad echocardiogram-based definition of PH, we found an overall incidence of PH at 28 days of age with the highest incidence occurring in infants with severe BPD. These results suggest that even subtle signs of early pulmonary vascular disease in the first month after birth, as evidenced by echocardiographic markers, are associated with increased duration of oxygen support.

A limitation of this study was the single center and retrospective nature. Also, the lack of confirmation and quantification of PH by right heart catheterizations is a limitation, and cardiac catheterization is the gold standard for the diagnosis of PH; however, this procedure is very invasive and is not practical in the NICU. Electrocardiography and echocardiography may be used as screening methods for PH; however, electrocardiography has low sensitivity and positive predictive value for the diagnosis of right ventricular hypertrophy, although it can be easily performed. Therefore, echocardiography, in spite of its several limitations, is recommended as the main screening tool for PH in BPD patients in many centers.

Overall, these findings support the hypothesis that early PH in preterm infants and long-term infection in preterm infants contributes to increased susceptibility for severe BPD. These data may further provide useful prognostic information for parents and suggest that routine echocardiographic screening may identify preterm infants who are at increased risk of late cardiopulmonary morbidities. In addition, early identification of preterm infants at greater risk for respiratory morbidities may allow the opportunity to better study novel interventions for BPD prevention.<sup>19</sup>

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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