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Risk Factors for Pulmonary Artery Hypertension in Preterm Infants with Moderate or Severe Bronchopulmonary Dysplasia

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Key Words
Risk factor · Pulmonary artery hypertension · Bronchopulmonary dysplasia

Abstract
Background: Despite the potential importance of pulmonary artery hypertension (PAH) in preterm infants with bronchopulmonary dysplasia (BPD), little is known about the risk factors for PAH. ***Objectives:*** To investigate the risk factors for PAH in preterm infants with BPD. ***Methods:*** Infants diagnosed with BPD were assigned to the PAH group or non-PAH group except for infants with mild BPD who had no PAH. PAH was diagnosed on the basis of echocardiograms demonstrating elevated right ventricle pressure beyond the postnatal age of 2 months. Logistic regression analysis was done for the multivariate assessment of the risk factors for PAH in preterm infants with moderate or severe BPD. ***Results:*** A total of 98 infants among 145 infants with BPD were divided into a PAH group (n = 25) or non-PAH group (n = 73), while the remaining 47 infants had mild BPD with no PAH. Among the study patients, survival rate of the PAH group was significantly lower than that of the non-PAH group. Infants with PAH had more severe cases of BPD and underwent longer durations of oxygen therapy, conventional or high-frequency ventilation, and hospitalization compared to those without PAH. Low 5-min Apgar scores (≤6; relative risk (RR) 6.2; 95% confidence interval (CI) 1.4–28.0; p = 0.017) and oligohydramnios (RR 7.7; 95% CI 2.0–29.6; p = 0.030) were found to be significant risk factors for PAH according to multivariate analysis. ***Conclusions:*** The present study shows that oligohydramnios is a specific risk factor for PAH in preterm infants with moderate or severe BPD.

Introduction

The pathophysiology of bronchopulmonary dysplasia (BPD) has evolved from its classical form following the introduction of antenatal glucocorticoid, surfactant replacement therapy, and gentler ventilatory support since the disease condition was originally described by Northway in 1967 [1–4]. Recently, the impact of antenatal lung injury and inflammatory response, and the mechanism underlying the priming effect of antenatal inflammation on the pathogenesis of current forms of BPD have been investigated [5, 6]. Despite this evolution, BPD still remains a major chronic pulmonary complication in small preterm infants [7]. Although most studies of BPD have

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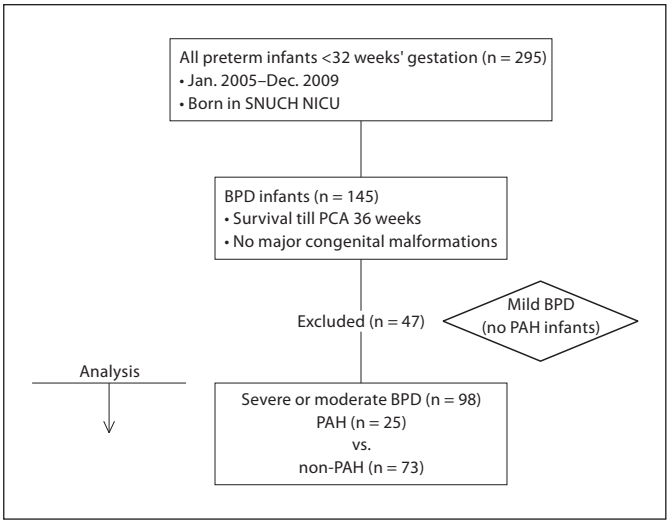

Fig. 1. Flow diagram showing the study design of the 145 infants with BPD and PAH enrolled in this study. SNUCH = Seoul National University Children's Hospital.

focused primarily on airway pathologies, infants with BPD are also at high risk of cardiovascular sequelae such as pulmonary artery hypertension (PAH), left ventricular hypertrophy, systemic hypertension, systemic to pulmonary collateral vessels, and others [8].

Early injury to the lung circulation leads to the rapid development of PAH after premature birth [8]. According to several small studies concerning the outcomes of infants with PAH and BPD, a quarter of BPD infants later show echocardiographic evidence of PAH [9, 10]. Although the exact mechanisms responsible for pulmonary vascular resistance remain incompletely understood, PAH in BPD results from increased vascular tone and abnormal vasoreactivity, hypertensive remodeling, and decreased vascular growth [8, 11]. The development of PAH is sometimes a serious complication of BPD that can significantly impact the morbidity and mortality rates of preterm infants [12–14].

Currently, there are few published studies about the clinical course and outcomes of PAH in preterm infants with BPD [15]. Despite the potential importance of PAH in preterm infants, little is also known about the risk factors for PAH in preterm infants with BPD. A lack of information about the risk factors for PAH complicates development of appropriate screening guidelines for PAH in preterm infants with BPD. The objective of this study was to investigate the risk factors for PAH in preterm infants with BPD in the postsurfactant era.

Methods

The study was approved by the institutional research ethics committee at Seoul National University Hospital.

Patients

A retrospective review was performed of data from 295 infants with a gestational age of <32 weeks born in the neonatal intensive care unit (NICU) at Seoul National University Children's Hospital during a 5-year period (January 2005 to December 2009). Infants with major congenital malformations (e.g. documented chromosomal anomaly or multiple malformations) and infants who died before reaching a postconceptional age (PCA) of 36 weeks were excluded (n = 30). Infants diagnosed with BPD were assigned to the PAH group or non-PAH group except for infants with mild BPD who had no PAH. Data on the patients' clinical characteristics and outcomes were collected and analyzed retrospectively. A flow diagram showing the study design involving the 295 infants enrolled in this study is presented in figure 1.

Clinical characteristics were evaluated by a single reviewer directly from medical records. Clinical characteristics studied included birth weights <3rd percentile for age, preterm premature rupture of membrane (PPROM, rupture of membranes before 37 completed weeks of gestation and 24 h prior to delivery), histologic chorioamnionitis (HCAM, presence of acute inflammatory changes on examination found up on a membrane roll and the placental chorionic plate), prenatal steroids (any dose of steroids including either a partial or completed course), and oligohydramnios (defined as amniotic fluid index <5 cm by ultrasound performed just before delivery [16]).

BPD and its severity were defined using the criteria of the National Institute of Child Health Workshop definition for BPD [17], i.e. treatment with oxygen for at least 28 days with division into the following three subgroups at 36 weeks' PCA: (1) mild (breathing room air); (2) moderate (need for a <30% fraction of inspired oxygen (FiO_2)), and (3) severe (need for ≥30% fraction of inspired oxygen and/or positive pressure support). A diagnosis of respiratory distress syndrome (RDS) required the presence of respiratory distress, increased oxygen requirement and a radiological finding consistent with RDS in the absence of evidence of any other cause of respiratory distress. Intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC) were classified using the Volpe grading system and modified Bell's staging criteria, respectively [18, 19]. Presence of proven sepsis was defined as at least a single blood culture and clinical signs of infection. Patent ductus arteriosus (PDA) was diagnosed by echocardiography.

Pulmonary Artery Hypertension

In the cardiologic division of Seoul National University Children's Hospital, we conducted monthly echocardiographic examination of the preterm infants with BPD in the NICU to screen for PAH and of the follow-up patients with moderate to severe BPD after discharge from the hospital even though the patients did not have PAH while in the NICU. PAH was diagnosed on the basis of echocardiograms demonstrating elevated right ventricle (RV) pressure using the following criteria: (1) velocity of tricuspid valve regurgitation of ≥3 m/s in the absence of pulmonary stenosis, and (2) flat or leftward deviated interventricular septal configuration, and right ventricular hypertrophy with chamber dilation. Patients with one or both of these findings beyond 2 months of

age were characterized as having PAH. Patients with PAH that persisted beyond 2 months of age with echocardiographic evidence of PAH before 2 months of age were included in this study. Patients with congenital heart disease (except those with a patent foramen ovale, PDA, or atrial septal defect), persistent pulmonary hypertension of the newborn, or congenital diaphragmatic hernia were excluded.

Data Analyses

To investigate the impact of PAH on the outcomes of preterm infants with BPD, we performed univariate analyses for the following variables: durations of oxygen therapy, conventional or high-frequency ventilation, and hospitalization, weight <3rd percentile for age at discharge, and expired patients after PCA 36 weeks.

Next, in an attempt to define the roles of different risk factors associated with the development of PAH in preterm infants with BPD, we performed univariate analyses to compare the following variables which are presumed to be associated with the development of PAH in infants with or without PAH as reported in previous studies [11, 15, 20]: gender, multiple births, mode of delivery, gestational age, birth weight, birth weight <3rd percentile for age, low 5-min Apgar scores (≤6), PPROM, HCAM, prenatal steroids administration, preeclampsia, oligohydramnios, RDS, PDA, IVH (Gr ≥3), NEC (stage ≥2), and proven sepsis. The univariate analyses were followed by a multivariate logistic regression analysis to determine independent risk factors for the development of PAH. Variables that were significant in the previous univariate analyses were chosen to be included in the logistic regression model. For this analysis, we used the binary logistic regression procedure. Using this analytic method, we evaluated the contribution of each variable to the logistic regression model and selected the ones whose contribution was significant independent of the effect of the other variables in the model. Next, we calculated the adjusted relative risks (RR) for the development of PAH and the 95% confidence intervals (CI) of the selected variables.

Statistical analyses were performed using SPSS for Windows, version 12.0 (SPSS Inc., Chicago, Ill., USA). Categorical variables were analyzed by the χ^2 test and Fisher's exact test. Differences in continuous variables were assessed by Student's t test and the Mann-Whitney U test. Time-dependent outcomes were assessed using Kaplan-Meier analysis, with comparison between two groups using the log-rank test. Data are presented as mean ± SD or frequency. p values <0.05 were considered significant.

Results

Of the 295 infants enrolled in the present study, 145 (49%) were diagnosed as having BPD. A total of 25 preterm infants (17 males and 8 females) with BPD had PAH. PAH was diagnosed in 52.5% (21/40) of infants with severe BPD, 6.9% (4/58) of infants with moderate BPD, and 0% (0/47) of infants with mild BPD. Risk for the development of PAH in infants with severe BPD was 7.6 times higher than those with moderate BPD (p = 0.000). PAH was diagnosed at a median age of 90 days (range 33–250). Except for 47 infants with mild BPD that had no PAH among these 145 infants, a total of 98 infants were divided into the PAH group (n = 25) or non-PAH group (n = 73) (table 1).

In all subjects, infants with PAH had a greater need for ≥30% FiO_2 or positive pressure support at PCA 36 weeks, suggesting severe BPD (p = 0.000) and longer durations of oxygen therapy (p = 0.011), conventional or high-frequency ventilation (p = 0.032), and hospitalization (p = 0.022) compared to those without PAH (table 1). Five patients (20%) in the PAH group died during the follow-up period in contrast with 1 patient (1%) in the non-PAH group who died. Among with all subjects, the average survival rate of the PAH group was significantly lower than that of the non-PAH group (p = 0.011) (fig. 2).

Univariate analysis for the comparison of clinical characteristics according to the presence or absence of PAH in all subjects included in this study showed a statistically significant difference ($p < 0.05$) in three variables (table 1): birth weight <3rd percentile for age (28 vs. 10%, p = 0.031), low 5-min Apgar scores (≤6; 88 vs. 63%, p = 0.015), and oligohydramnios (40 vs. 8%, p = 0.001). We investigated the specific risk factors for the development of PAH by multivariate logistic regression analysis with adjustment for variables which were significant in the previous univariate analysis. In all subjects, low 5-min Apgar scores (≤6; RR 6.2; 95% CI 1.4–28.0; p = 0.017) and oligohydramnios (RR 7.7; 95% CI 2.0–29.6; p = 0.030) were found to be significant risk factors for PAH after adjusting for birth weight <3rd percentile for age, low 5-min Apgar scores (≤6), and oligohydramnios (table 2). Univariate analysis in a total of 40 infants with severe BPD showed a statistically significant difference in two variables: low 5-min Apgar scores (≤6) and oligohydramnios. In addition, in the multivariate analysis, low 5-min Apgar scores (≤6; RR 7.8; 95% CI 1.2–52.0; p = 0.034) and oligohydramnios (RR 7.2; 95% CI 1.1–47.3; p = 0.040) were also significant risk factors for PAH after adjusting for low 5-min Apgar scores (≤6) and oligohydramnios.

Discussion

In the present study, most of the infants diagnosed as having PAH had underlying severe BPD (84%, 21/25) and none of them had underlying mild BPD. This proportion of infants with underlying severe BPD among ones diagnosed as having PAH was much higher than the 41% reported in a recent study [15]. We excluded infants with mild BPD from our study because the inclusion of infants

Table 1. Univariate analysis of clinical characteristics according to the presence or absence of PAH in all subjects of this study

Clinical characteristics	All study patients (n = 98)	PAH (n = 25)	Non-PAH (n = 73)	p values
Male	61 (62)	17 (68)	44 (60)	NS
Multiple births	51 (52)	8 (32)	40 (55)	NS
Cesarean section	68 (69)	19 (76)	49 (67)	NS
Gestational age, weeks	26.8 ± 1.9	26.9 ± 2.4	26.4 ± 1.9	NS
Birth weight, g	835 ± 228	765 ± 237	799 ± 234	NS
Birth weight <3rd percentile for age	14 (14)	7 (28)	7 (10)	0.031
5-min Apgar scores, ≤6	68 (69)	22 (88)	46 (63)	0.015
PPROM	43 (44)	13 (52)	30 (41)	NS
HCAM	29 (30)	5 (20)	24 (33)	NS
Prenatal steroids administration	70 (71)	16 (64)	54 (74)	NS
Preeclampsia	16 (16)	7 (28)	9 (12)	NS
Oligohydramnios	16 (16)	10 (40)	6 (8)	0.001
RDS	58 (59)	15 (60)	43 (59)	NS
PDA	93(95)	23 (92)	70 (96)	NS
IVH, Gr ≥3	14 (14)	4 (16)	10 (14)	NS
NEC, stage ≥2	13 (13)	4 (16)	9 (12)	NS
Proven sepsis	32 (33)	9 (36)	23 (32)	NS
Need for ≥30% FiO_2 or positive pressure support at PCA 36 weeks	40 (41)	21 (84)	19 (26)	0.000
Duration of O_2 therapy, days	106 ± 52.8	141 ± 84.3	93.5 ± 28.4	0.011
Duration of CV or HFV, days	50.8 ± 55.6	82.5 ± 92.3	39.9 ± 29.2	0.032
Duration of hospitalization, days	116 ± 52.1	147 ± 83.5	105.5 ± 29.8	0.022
Weight <3rd percentile for age at discharge	51/92 (55)	13/20 (65)	38/72 (53)	NS
Expired after PCA 36 weeks	6 (6)	5 (20)	1 (1)	0.004

Values are expressed as mean ± SD or numbers of individuals with percentages in parentheses.

p values: PAH group vs. non-PAH group.

NS = Not significant; PPROM = preterm premature rupture of membrane; HCAM = histologic chorioamnionitis; RDS = respiratory distress syndrome; PDA = patent ductus arteriosus; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; FiO_2 = fraction of inspired oxygen; PCA = postconceptional age; CV = conventional ventilation; HFV = high-frequency ventilation.

with mild BPD having no PAH could make it difficult to identify the risk factors for PAH.

It has been reported that the mortality rate for PAH among preterm infants with BPD is very high. Two studies published in the 'presurfactant era' showed mortality rates of 50 and 29%, respectively, in infants with BPD and PAH [12, 13]. Additionally, in the 'postsurfactant era', PAH with BPD was strongly associated with poor survival with a recent report showing a mortality rate of 38% for infants with PAH [15]. Contrary to our study, all of the reports mentioned above did not compare the mortality rates of infants with PAH to non-PAH patients. In the present study, a mortality rate of 20% associated with PAH was significantly higher than the 1% observed in infants without PAH but with moderate or severe BPD. In addition, given that infants with PAH have more severe cases of BPD and longer durations of oxygen therapy, conventional or high-frequency ventilation, and hospitalization than those without PAH, PAH may be a serious factor impacting the outcomes of BPD.

Recent experimental studies have shown that early injury to the developing lung can impair angiogenesis which further contributes to decreased alveolarization and simplification of distal lung airspace, leading to the development of BPD (the 'vascular hypothesis') [21–23]. It is also speculated that reciprocal interactions exist between the developing airspace and pulmonary circulation [24]. Abnormal lung circulation in BPD patients, including both anatomical and physiologic abnormalities, is related to the development of PAH. Patients with BPD show a reduction of small pulmonary arteries and an altered distribution of pulmonary arteries within the pulmonary interstitium that cause reduction of the alveolar-capillary surface area [2, 25]. This reduction in surface

Table 2. Risk factors for the development of PAH in each group determined by binary logistic regression analysis

Clinical characteristics	Unadjusted RR (95% CI)	p values	Adjusted[1] RR (95% CI)	p values
Birth weight <3rd percentile for age	2.9 (1.1–7.5)	0.031	3.0 (0.1–1.9)	0.282
5-min Apgar scores, ≤6	1.4 (1.1–1.8)	0.015	6.2 (1.4–28.0)	0.017
Oligohydramnios	4.9 (2.0–12.0)	0.001	7.7 (2.0–29.6)	0.030

[1] Adjusted for birth weight <3rd percentile for age, 5-min Apgar scores (≤6), and oligohydramnios in all subjects included in this study.

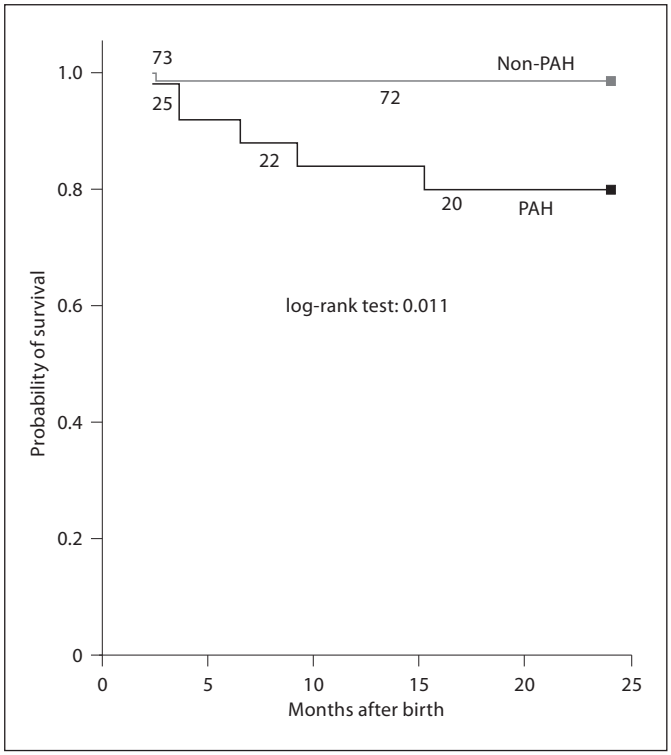

Fig. 2. Kaplan-Meier curve demonstrating the probability of survival from the time of birth for the study patients with moderate or severe BPD (n = 98), including infants with PAH (n = 25) and those without PAH (n = 73). Survival rate of the PAH group was significantly lower than that of the non-PAH group (p = 0.011). The numbers of infants that survived are indicated along the respective curves.

area leads to impaired gas exchange and increases the requirement for prolonged oxygen and ventilator treatment which in turn raises the risk of severe PAH [11]. In the present study, low 5-min Apgar scores (≤6) and oligohydramnios were significant independent risk factors for PAH in all subjects with moderate or severe BPD. To identify the risk factors for PAH with BPD regardless of its severity, we performed additional analyses on the subjects with severe BPD but not those with moderate BPD. In these analyses, 5-min Apgar scores (≤6) and oligohydramnios were also significant independent risk factors for PAH. The notable finding of the present study is that oligohydramnios was the specific risk factor for PAH in preterm infants with BPD. Oligohydramnios is likely to influence growth and morphogenesis of the developing lung. Furthermore, a retrospective study conducted in infants with a gestational age of <37 weeks who had an echocardiographic diagnosis of PAH within the first 4 weeks of life also suggested that oligohydramnios was independently predictive of PAH [20]. Normal transition from the canalicular stage to the saccular stage of development requires the production of fluid by the fetal lung. Lung fluid is kept pressurized by a combination of laryngeal closure and fluid production by the respiratory epithelia. The pressure of fetal lung fluid is important for lung growth as illustrated by the pulmonary hypoplasia seen in neonates with oligohydramnios [26–28]. Preterm infants with hypoplastic lungs may have elevated pulmonary vascular resistance; this may be related to maldevelopment including a decrease in the cross-sectional area and abnormal muscularization of the pulmonary vasculature [28–30]. Although there was no evidence of definite hypoplastic lungs in infants according to our study, some inhibitive effect of oligohydramnios on lung development might influence the development of PAH in preterm infants with BPD. Altogether, our results suggest that oligohydramnios may contribute to vascular arrest as well as alveolar arrest during fetal lung development, and furthermore result in the subsequent development of PAH in BPD patients. This corresponds to the 'vascular hypothesis' of BPD. In the present study, a low 5-min Apgar score (≤6) was another specific risk factor for PAH in

preterm infants with BPD. Some researchers reported that oligohydramnios is associated with an increased risk of adverse perinatal outcome [31, 32]. In one meta-analysis, infants with oligohydramnios had a 5.2-fold increased risk for a 5-min Apgar score of <7 [31]. Based on these previous studies, it is assumed that low 5-min Apgar scores (≤6) found to be a PAH risk factor can be the consequence of oligohydramnios. Meanwhile, Khemani et al. [15] reported that among 18 patients with severe PAH (systemic or supra-systemic RV pressure) almost half were born with weight <3rd percentile for age, which suggests that birth weight <3rd percentile for age may be at increased risk for severe PAH. This same group [15] also reported that birth weight <3rd percentile for age with severe PAH is associated with worse survival rates in multivariate analyses, However, in the present study birth weight <3rd percentile for age was associated with the development of PAH in the univariate analysis but not in the multivariate analysis.

In the present study, the diagnosis of PAH depended entirely on echocardiography. Cardiac catheterization has been accepted as the gold standard for diagnosing PAH to date. However, since this procedure is very invasive and is not easily performed in the preterm cases in NICU, serial echocardiography is recommended as the main tool to screen for PAH in BPD patients despite its several limitations [11, 33]. In the present study, it was found that echocardiography is a useful tool for diagnosing PAH and predicting the outcomes in infants with BPD in clinical setting.

In summary, among infants with moderate or severe BPD, the survival rate of ones with PAH was significantly lower than that of infants who did not. Furthermore, the infants with PAH had to undergo longer durations of oxygen therapy, conventional or high-frequency ventilation, and hospitalization than those without PAH. Oligohydramnios was a specific risk factor for PAH in preterm infants with moderate or severe BPD. We therefore suggest that a more active screening echocardiogram may be needed for diagnosing PAH in preterm infants with moderate or severe BPD, especially in the setting of oligohydramnios. Further large cohort studies will be required to confirm our results and identify other risk factors for the development of PAH in infants with BPD.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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