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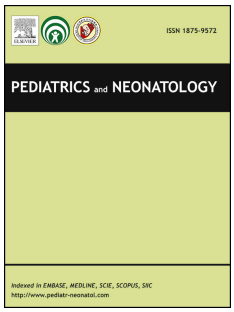

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Title

The Impact of Atrial Left-to-Right Shunt on Pulmonary Hypertension in Preterm Infants with Moderate or Severe Bronchopulmonary dysplasia

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Abstract

Background: Although bronchopulmonary dysplasia (BPD)-associated pulmonary hypertension (PH) is a well-known complication of prematurity, the additional impact of left-to-right interatrial shunt on this condition remains poorly understood. The aim of the present study was to identify the significance of atrial left-to-right shunt lesions in PH infants with moderate or severe BPD.

Materials and Methods: The medical records of 383 preterm infants (<32 weeks' gestational age) diagnosed with BPD between 2005 and 2013 were retrospectively reviewed. Baseline characteristics, including interatrial shunts and outcomes, were compared between the infants who developed PH (n = 50) and those who did not (n = 144). Infants with hemodynamically significant residual PDAs were excluded. Among the infants diagnosed with PH (n = 50), the outcomes were compared between the subjects with (n = 21) and without atrial shunts (n = 29) at 36 weeks' corrected postmenstrual age (PMA).

Results: Fifty infants (15%) of the preterm infants with BPD were diagnosed with PH. The number of infants with a history of atrial shunt lesions was significantly higher in the PH group compared to the non-PH group (42% vs. 15.3%, respectively). The adjusted odds ratio for PH in the atrial shunt group was 3.8 (95% confidence interval, 1.8 to 8.0) compared to PH-BPD infants without atrial shunt.

Conclusion: The presence of an atrial left-to-right shunt was associated with PH in preterm infants with moderate or severe BPD. Close follow-up is needed for infants with interatrial shunts, and more tailored prognostic evaluation and treatment are recommended.

Keywords

atrial septal defect; bronchopulmonary dysplasia; congenital heart disease; pulmonary hypertension; premature infant

1. Introduction

Despite advances in critical care management, chronic pulmonary morbidity is a common adverse outcome in preterm neonates, particularly in preterm infants who develop bronchopulmonary dysplasia (BPD).[1] Pulmonary hypertension (PH) is a major cause of late mortality in preterm infants with BPD.[2] Previous retrospective studies have reported PH-associated mortality rates ranging between 14 and 38% in preterm infants with BPD. The only currently published prospective study has reported a prevalence of 18% and a mortality rate of 11.5% for extremely low-birth-weight infants. Survivors are at an increased risk of long-term morbidity, including long hospitalization durations and oxygen therapy.[3-5]

The pathogenesis of PH in infants with BPD is multifactorial, and infants with BPD may develop PH due to early damage to pulmonary angiogenesis, which could be exacerbated by inflammation,[6] lung and airway injuries,[7] cardiac shunts, diastolic cardiac dysfunction and pulmonary vein stenosis.[8] The previous studies have reported that infants with PH frequently had a history of minor cardiac anomalies, and it was suggested that infants with chronic lung disease (CLD) and shunt lesions might be at an increased risk for PH.[9,10] It was suggested that even minor increases in left-to-right shunting of the blood through atrial defects might induce a significant hemodynamic injury and aggravate PH because of the reduced vascular surface area in the lungs of infants with BPD.[11] However, the exact significance of this minor cardiac anomaly is unknown.[12]

The present study was conducted to investigate the clinical impact of atrial left-to-right shunts on PH prevalence in preterm infants with severe or moderate BPD.

Materials and Methods

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

1.1. Patients and definitions

We retrospectively reviewed the medical records of preterm infants who were born at <32 weeks' gestational age and admitted to the neonatal intensive care unit (NICU) at Seoul National University Children's Hospital between January 2005 and March 2013. Overall, 383 preterm infants were diagnosed with BPD during the study period. Infants with major congenital heart diseases (except for patent ductus arteriosus (PDA), patent foramen ovale, and atrial septal defect (ASD)), chromosomal abnormalities, congenital diaphragmatic hernia, and persistent pulmonary hypertension were excluded. Infants who were transferred to our hospital after 36 weeks' corrected postmenstrual age (PMA) or who died before 36 weeks' PMA were also excluded (n=49).

The clinical data collected included birth weight, gestational age, prenatal steroids (administration of any dose of corticosteroids during the concurrent pregnancy), histological chorioamnionitis (based on the pathological findings from the microscopic examination of the placenta), PDA and its treatment, BPD and its grade, and culture proven-sepsis. PDA cases that were treated with cyclooxygenase inhibitors or surgical ligation and hemodynamically significant residual PDAs after 36 weeks' PMA were excluded. BPD was defined using the National Institute of Child Health criteria for BPD and graded as mild, moderate, or severe, according to the fraction of inspired oxygen (FiO2) or positive pressure

ventilation (PPV). Mild BPD was defined as breathing room air; moderate BPD was defined as FiO2 < 0.30, and severe BPD was defined as FiO2 ≥ 0.30 or PPV at 36 weeks' PMA. Serial echocardiographic data for all preterm infants with moderate to severe BPD were reviewed, including evaluations with 2-dimensional, M-mode, and color-coded Doppler by a pediatric cardiologist at Seoul National University Children's Hospital. Infants were diagnosed with PH if an echocardiogram performed when they were older than 2 months of age demonstrated elevated pulmonary artery pressure based on the presence of at least one of the following criteria: 1) velocity of tricuspid valve regurgitation (TR) ≥ 3 m/s in the absence of pulmonary stenosis or 2) flat or left-deviated interventricular septal configuration and right ventricular hypertrophy with chamber dilation.[13,14] Data on the infants' interatrial shunts at 36 weeks' PMA were collected and followed-up using echocardiography. We recorded the final diagnoses of the atrial shunts (ASD or PFO), which were still open at the corrected postnatal age of 2 months.[15]

1.2. Statistical analysis

All data analysis was performed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed using either the t-test or the Mann-Whitney U-test for normal or skewed distributions, respectively. Proportions were tested using the chi-squared test and the Fisher exact test, and p values of < 0.05 were considered to be significant. The significant variables identified by univariate analysis were further assessed with multivariable logistic regression analysis. Data are presented as the mean ± SD, median and range, or rate. Odds ratios are presented with 95% confidence intervals.

Results

Patients

Of the total 383 preterm infants with BPD who were born at <32 weeks' gestational age, 5 infants were excluded because of death prior to 36 weeks' PMA; 29 infants were excluded due to major congenital malformation, and 15 infants were excluded because of incomplete follow-up data. The remaining 334 preterm infants with BPD fulfilled the inclusion criteria. A flow diagram is presented in Figure 1.

Pulmonary hypertension with moderate or severe bronchopulmonary dysplasia

Among the 334 infants with BPD, 50 infants (15%) were diagnosed with PH. PH was diagnosed in 54% (45/83) of the infants with severe BPD, 4% (5/111) of the infants with moderate BPD, and 0% (0/140) of the infants with mild BPD. Except for the infants with mild BPD, the clinical characteristics and outcomes for the infants with (n = 50) and without PH (n = 144) are presented in Table 1. According to the PH diagnostic criteria, systolic PAP could be estimated in 64% of infants (n = 32) by measurable TR. The median measurable TR in PH infants was 3.4 m/sec (range, 3.0-4.2 m/sec). We used the modified Bernoulli equation to convert Doppler-derived velocity to pressure (pressure gradient between the right ventricle and right atrium = 4 x [TR max^2]) (median, 46.2 mm Hg; range, 36.0-70.6 mm Hg). For the other 36% of the infants (n = 18) with PH, qualitative echocardiographic measures of PH in the absence of measureable TR, such as septal flattening, right atrial enlargement, right ventricular hypertrophy, and right ventricular dilatation, were used as diagnostic tools. Only 2 infants in the PH group and 1 infant in the non-PH group had small residual PDAs at 36

weeks' PMA; however, these small residual PDAs were hemodynamically insignificant and were immediately closed before discharge.

The infants with PH spent more days on a mechanical ventilator ($p < 0.001$), including high frequency ventilators (HFV), but fewer days on nasal continuous positive airway pressure (nCPAP) ($p < 0.001$) compared to infants in the non-PH group. Three infants in the PH group died during hospitalization, but there were no deaths in the non-PH group ($p = 0.016$). The causes of death for the three infants were respiratory failure despite mechanical ventilation and a high fraction of O2. The median duration of hospitalization was longer in the PH group compared to the non-PH group ($p = 0.04$). The majority of infants in the PH group required prolonged oxygen therapy at discharge compared with the non-PH group (80% vs. 35.4%, respectively) ($p < 0.001$).

Multivariate analysis was performed to investigate the risk factors for PH. The results after adjusting for variables that were significant in the previous univariate analysis revealed that the significant risk factors for PH were proven sepsis (adjusted OR 3.5; 95% CI, 1.7-7.2; $p = 0.001$) and interatrial shunts (adjusted OR 3.8; 95% CI, 1.8-8.0; $p < 0.001$) (Table 2).

Comparison of PH-BPD infants with and without atrial left-to-right shunt

We obtained a median 968 days (range, 64-2,875 days) of follow-up data after the diagnosis of PH. The median postnatal age at the initial diagnosis of PH was 87.5 days (range, 7-882 days) in the PH group. The median age at the PH diagnosis in the atrial shunt group was significantly earlier than that in the non-atrial shunt group (62 days vs. 103 days, $p = 0.004$).

Major morbidities and outcomes were compared between infants with ($n = 21$) and without atrial shunts ($n = 29$) (Table 3). The hospitalization duration ($p = 1.000$), O2 therapy ($p = 0.567$), mechanical ventilation ($p = 0.589$) and nCPAP ($p = 0.252$) did not differ significantly

between the two groups. However, the mortality rate of the PH-BPD infants with atrial shunts was significantly higher than that of the PH-BPD infants without atrial shunts (14.3% vs. 0%, respectively, p = 0.026). During the follow-up period, 4 infants in the atrial shunt group died, including 3 infants who died during hospitalization and 1 infant who died suddenly at home two days after being discharged without any improvement in PH.

In our hospital, management for PH in BPD infants includes inhaled NO, sildenafil, bosentan, and inhaled iloprost. Eighteen infants (85.7%) in the atrial shunt group received at least one of these pulmonary vasodilator therapies during the follow-up period, while only 17 infants (58.6%) in the non-atrial shunt group received these therapies (p = 0.038). Sildenafil was administered most often. In each group, the following drugs were administered: atrial shunt group, inhaled NO, 7 (33.3%), sildenafil, 17 (81.0%), bosentan, 3 (14.2%), and iloprost 6 (28.6%); in the non-atrial shunt group, inhaled NO, 9 (31.0%), sildenafil, 16 (55.2%), bosentan, 1 (3.4%), and iloprost 1 (3.4%). Seventy-four percent of infants in the atrial shunt group and 90% of infants in the non-atrial shunt group ceased oxygen supplementation 1 year after the initial diagnosis of PH; however, these data were not statistically significant (p = 0.327).

Among the PH-BPD infants with interatrial shunts, 62% (n = 13) were finally diagnosed with ASDs and 24% (n = 5) with PFOs after a corrected postnatal age of 2 months. At the final follow-up assessment, 67% of these defects (n = 14) had spontaneously closed, and 14% of the infants (n = 3) underwent a primary closure operation for ASD.

Discussion

To our knowledge, this report is the first to directly investigate the association between atrial left-to-right shunts and PH in premature infants with BPD. Mourani et al.[9] reviewed the medical charts of the children diagnosed with CLD and who underwent cardiac catheterization for PH evaluation. Specifically, the authors reported that 68% of the patients had a history of shunt lesions, primarily atrial shunts, which were detected in 58% of this subgroup of patients. The authors also noted the impact of left-to-right shunt lesions in children with CLD and suggested early treatment considerations for pulmonary overcirculation. The incidence of atrial left-to-right shunt was 42% at 36 weeks' PMA among the BPD-PH infants in our institution; and 67% of these defects were found to have spontaneously closed by the last follow-up. A total of 3 infants with left-to-right shunts through moderate-sized ASD underwent primary closure operations, with positive results. The sizes of each ASD at 36 weeks' PMA were 4 mm, 4.67 mm, and 5.5 mm, respectively. These infants showed improved respiratory functions after the shunts were closed; however, severe PH persisted, despite the administration of PH-specific drugs. We demonstrated that the presence of a left-right shunt flow over the atrial septum in moderate or severe BPD infants was associated with development of PH compared to infants without atrial shunt.

In general, patients with large and complex defects are at the greatest risk for PH compared to pre-tricuspid shunt patients (i.e., ASD), who generally never develop PH.[16,17] Atrial left-to-right shunts are frequently detected during routine cardiac screening in BPD infants in neonatal intensive care units,[15] and the high rate of spontaneous closure or decrease in the size of the atrial defect in the first months of life is frequently observed.[18] For this reason, it is unusual to require closure of an ASD in infants without associated lung disease.[19] However,

poorer lung compliance in premature infants could prevent or delay closure of the interatrial septum due to greater phasic respiratory changes in intrathoracic, left atrial and right atrial pressures.[20] If there are persistent left-to-right cardiac shunts in BPD lungs, small shunts can have a greater impact on pulmonary blood flow and aggravate PH because the lungs have an overall reduction in alveolar-capillary surface area with vascular remodeling.[10,12] Moreover, PH might be exaggerated by vascular abnormalities, such as pulmonary vein stenosis, which often occur in association with left-to-right cardiac shunts.[21,22] Based on the findings from our study and previously published reports describing success in closing ASD in patients with CLD,[22-25] we suggest that early management, including closure of the ASDs, should be considered as an optional treatment in infants with moderate or large atrial shunt lesions who are unresponsive to traditional PH therapies. Close follow-up is needed to evaluate the severity of PH by echocardiography, and diuretics, which reduce pulmonary overflow, can be considered to relieve acute respiratory symptoms. The addition of biomarkers, such as brain natriuretic peptide levels, would also be useful for serial follow-ups. Cardiac catheterization is needed for infants with a history of atrial left-to-right shunts and persistent signs of severe cardiorespiratory disease, and it is important to select infants with BPD who would benefit from closing the left-to-right shunts.[26] Early assessment and intervention of anatomic cardiac lesion can decrease the incidence of adverse outcomes, including heart failure.

In the current study, culture proven sepsis was a specific risk factor for PH in preterm infants with moderate or severe BPD. Forty-six percent of preterm infants with PH had a history of proven sepsis, which was significantly greater than the number of infants with moderate or severe BPD without PH. This result closely aligns with those of earlier studies that reported that infectious respiratory illnesses were triggers for PH, particularly if the infant was oxygen-dependent.[13,27]

Our study is limited by its retrospective design. The time of diagnosis may not be accurate because the evaluation interval was determined based on the infant's condition. Echocardiography is not the gold standard for assessing pulmonary artery pressure (PAP). The assessment of atrial shunt was a quantitative one, and we did not have data on the quality of the shunt lesions to assess the patient-specific hemodynamics of each defect. Echocardiography alone could not accurately determine the hemodynamic impact of small atrial defects. Although a significant difference was noted between the mortality rates of PH-BPD infants with and without atrial left-to-right shunt, careful interpretation of the data was required because of our small sample size to assess this outcome; thus, additional larger studies are needed.

In conclusion, this study confirms that preterm infants with PH-BPD have higher rates of death and serious morbidities compared to infants without PH. We found that preterm infants with a history of atrial left-to-right shunts at 36 weeks' PMA had an increased likelihood of developing PH compared to infants without any cardiac shunts. Given the high incidence of small atrial left-to-right shunts in preterm infants, we propose a more tailored prognostic evaluation of and diagnostic intervention for BPD infants with cardiac shunt lesions. Additional prospective studies of the impact of cardiac shunt lesions in infants with BPD are needed to determine the risk factors for PH development in preterm infants with BPD.

Conflicts of interest

All authors declare no conflicts of interest.

Acknowledgements

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References

1 Greenough A. Long-term pulmonary outcome in the preterm infant. *Neonatology* 2008;**93**:324–7.

2 Subhedar NV. Recent advances in diagnosis and management of pulmonary hypertension in chronic lung disease. *Acta Paediatr Suppl* 2004;**93**:29–32.

3 Bhat R, Salas AA, Foster C, Carlo WA, Ambalavanan N. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. *Pediatrics* 2012;**129**:e682–9.

4 An HS, Bae EJ, Kim GB, Kwon BS, Beak JS, Kim EK, et al. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. *Korean Circ J* 2010;**40**:131–6.

5 Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro RV, Thomas KC, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. *Pediatrics* 2007;**120**:1260–9.

6 Kim DH, Kim HS. Serial changes of serum endostatin and angiopoietin-1 levels in preterm infants with severe bronchopulmonary dysplasia and subsequent pulmonary artery hypertension. *Neonatology* 2014;**106**:55–61.

7 Reyburn B, Martin RJ, Prakash YS, MacFarlane PM. Mechanisms of injury to the preterm lung and airway: implications for long term pulmonary outcome. *Neonatology* 2012;**101**:345–52.

8 Cerro MJ, Abman S, Diaz G, Freudenthal AH, Freudenthal F, Harikrishnan S, et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular

disease: Report from the PVRI Pediatric Taskforce, Panama 2011. *Pulm Circ* 2011;**1**:286–98.

9 Mourani PM, Sontag MK, Younoszai A, Ivy DD, Abman SH. Clinical utility of echocardiography for the diagnosis and management of pulmonary vascular disease in young children with chronic lung disease. *Pediatrics* 2008;**121**:317–25.

10 del Cerro MJ, Sabaté Rotés A, Cartón A, Deiros L, Bret M, Cordeiro M, et al. Pulmonary hypertension in bronchopulmonary dysplasia: clinical findings, cardiovascular anomalies and outcomes. *Pediatr Pulmonol* 2014;**49**:49–59.

11 Mourani PM, Mullen M, Abman SH. Pulmonary hypertension in bronchopulmonary dysplasia. *Prog Pediatr Cardiol* 2009;**27**:43–8.

12 Cantinotti M, Assanta N, Murzi B, Lopez L. Controversies in the definition and management of insignificant left-to-right shunts. *Heart* 2014;**100**:200–5.

13 Farquhar M, Fitzgerald DA. Pulmonary hypertension in chronic neonatal lung disease. *Paediatr Respir Rev* 2010;**11**:149–53.

14 Ambalavanan N, Mourani P. Pulmonary hypertension in bronchopulmonary dysplasia. *Birth Defects Res A Clin Mol Teratol* 2014;**100**:240–6.

15 Game E, Olsen MS, Johnsen SP, Hjortdal V, Andersen HØ, Nissen H, et al. How do we define congenital heart defects for scientific studies? *Congenit Heart Dis* 2012;**7**:46–9.

16 Polito A, Piga S, Cogo PE, Corchia C, Carnielli V, Da Frè M, et al. Increased morbidity and mortality in very preterm/VLBW infants with congenital heart disease. *Intensive Care Med* 2013;**39**:1104–12.

17 D'Alto M, Mahadevan VS. Pulmonary arterial hypertension associated with congenital heart disease. *Eur Respir Rev* 2012;**21**:328–37.

18 Hanslik A, Pospisil U, Salzer-Muhar U, Greber-Platzer S, Male C. Predictors of spontaneous closure of isolated secundum atrial septal defect in children: a longitudinal study. *Pediatrics* 2006;**118**:1560–5.

19 Driscoll D, Allen HD, Atkins DL, Brenner J, Dunnigan A, Franklin W, et al. Guidelines for evaluation and management of common congenital cardiac problems in infants, children, and adolescents. A statement for healthcare professionals from the Committee on Congenital Cardiac Defects of the Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1994;**90**:2180–8.

20 Riggs T, Sharp SE, Batton D, Hussey ME, Weinhouse E. Spontaneous closure of atrial septal defects in premature vs. full-term neonates. *Pediatr Cardiol* 2000;**21**:129–34.

21 Drossner DM, Kim DW, Maher KO, Mahle WT. Pulmonary vein stenosis: prematurity and associated conditions. *Pediatrics* 2008;**122**:e656–61.

22 Chakrabarti S, Mittal R, Gnanapragasam JP, Martin RP. Acquired stenosis of normally connected pulmonary veins. *Cardiol Young* 2007;**17**:322–7.

23 Thomas VC, Vincent R, Raviele A, Dieh H, Qian H, Kim D. Transcathter closure of secundum ASD in infants less than 12months of age improves symptoms of CLD. *Congenit Heart Dis* 2012;**7**:204–11.

24 Wood AM, Holzer RJ, Texter KM, Hill SL, Gest AL, Welty SE, et al. Transcatheter elimination of left-to-right shunts in infants with bronchopulmonary dysplasia is feasible and safe. *Congenit Heart Dis* 2011;**6**:330–7.

25 Lim DS, Matheme GP. Percutaneous device closure of atrial septal defect in a premature infant with rapid improvement in Pulmonary status. *Pediatrics* 2007;**119**;398.

26 Mourani PM, Sontag MK, Ivy DD, Abman SH. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. *J Pediatr* 2009;**154**:379–84.

27 Kumar VH, Hutchison AA, Lakshminrusimha S, Morin FC 3rd, Wynn RJ, Ryan RM. *J Perinatol* 2007;**27**:214–9.

Tables

Table 1 Univariate analysis of clinical characteristics of infants with and without pulmonary hypertension.

	Infants without pulmonary hypertension N = 144	Infants with pulmonary hypertension N = 50	P values
Gestational age, weeks. Mean	26.6 ± 1.9	26.2 ± 2.0	0.221
Birth weight, g Mean	825 ± 253	754 ± 227	0.08
Birth weight <10th percentile for age, n (%)	37 (25.5)	15 (30.0)	0.581
Multiple birth, n (%)	87 (60.4)	18 (36.0)	0.003
Cesarean section, n (%)	92 (63.9)	33 (66.0)	0.865
Perinatal steroids administration, n (%)	110 (76.9)	35 (77.8)	1.000
Chorioamnionitis ,n (%)	55 (38.2)	22 (47.8)	0.301
Atrial left-to-right shunt at 36 weeks' PMA, n (%)	22 (15.3)	21 (42.0)	<0.001
Morbidity and mortality			
RDS, n (%)	97 (67.4)	36 (72.0)	0.599
Treated PDA with medication or ligation	129 (89.6)	48 (96.0)	0.245

operation (%)			
BPD, n (%)			
severe/moderate	38/106 (26.4/73.6)	45/5 (90.0/10.0)	<0.001
IVH Gr 3 or 4	27 (18.87)	8 (16.0)	0.831
PVL	14 (9.7)	4 (8.0)	1.000
Culture proven sepsis, n (%)	27 (18.8)	23 (46.0)	<0.001
ROP operation, n (%)	55 (38.2)	24 (48.0)	0.245
Death, n (%)	0 (0)	3 (6.0)	0.016
Length of stay, median, days	99.3 (48-214)	112.0 (56-329)	0.04
Respiratory support			
Duration of O2 therapy, median, days	86.3 (1.0-214)	104 (48-456)	0.002
Duration of CV or HFV, median, days	34.4 (0-123)	69.4 (0-456)	<0.001
Duration of nCPAP, median , days	11 (0-64)	1.3 (0.0-49)	<0.001
Discharged home on oxygen, n (%)	51 (35.4)	40 (80.0)	<0.001

Data are presented as mean ± SD, median and range, or rate. RDS: respiratory distress syndrome, PDA: patent ductus arteriosus, BPD: bronchopulmonary dysplasia, IVH: intraventricular hemorrhage, PVL: periventricular leukomalacia, NEC: necrotizing

enterocolitis, ROP: retinopathy of prematurity, CV: conventional ventilation, HFV: high-frequency ventilation, nCPAP: nasal continuous positive airway pressure

Table 2 Multiple logistic analysis of pulmonary hypertension with moderate or severe bronchopulmonary dysplasia infants.

Clinical characteristics	Unadjusted OR (95% CI)	P values	Adjusted OR (95%CI)	P values
Proven sepsis	3.7 (1.8-7.4)	< 0.001	3.5 (1.7-7.2)	0.001
Atrial left-to-right shunt at 36 weeks' PMA	3.5 (1.7-7.0)	< 0.001	3.8 (1.8-8.0)	< 0.001

Table 3 Comparison of clinical outcomes between with and without atrial left-to-right shunts in PH-BPD infants.

	PH without atrial left-to-right shunt N = 29	PH with atrial left-to-right shunt N = 21	P values
Morbidity and mortality			
BPD, n (%)			
severe/moderate	27 / 2 (93.1 / 6.9)	18 / 3 (85.7 / 14.3)	0.638
Culture proven sepsis, n (%)	11 (37.9)	12 (57.1)	0.252
Treated PDA with medication or ligation operation (%)	27 (93.1)	19 (90.0)	0.993
Death, n (%)	0 (0)	3 (14.3)	0.026
Length of stay, median, days	112.0 (64.0-293.0)	111.0 (56.0-456.0)	1.000
Respiratory support			
Duration of O2 therapy, median, days	112.0 (65.0-293.0)	102.0 (48.0-456.0)	0.567
Duration of CV or HFV, median, days	69.0 (13.0-243.0)	69.7 (0-456.0)	0.810
Duration of nCPAP, median , days	20.0 (0-80.0)	6.3 (0-49.0)	0.252
Discharged home on oxygen, n (%)	24 (60.0)	16 (40)	0.692

Data are presented as median and range, or rate. PDA: patent ductus arteriosus, BPD: bronchopulmonary dysplasia, CV: conventional ventilation, HFV: high-frequency ventilation, nCPAP: nasal continuous positive airway pressure

Figure legends

Figure 1 Flow diagram of the study design. BPD: bronchopulmonary dysplasia, PMA: corrected postmenstrual age, PH: pulmonary hypertension