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ORIGINAL ARTICLE

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

Eui Kyung Choi [†], Young Hwa Jung [†], Han-Suk Kim*, Seung Han Shin, Chang Won Choi, Ee-Kyung Kim, Beyong Il Kim, Jung-Hwan Choi

Department of Pediatrics, Seoul National University College of Medicine, Seoul, South Korea

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Key Words
atrial septal defect;
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Background: Bronchopulmonary dysplasia (BPD)-associated pulmonary hypertension (PH) is a well-known complication of prematurity; however, the additional impact of a 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.

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

Results: Fifty (15%) 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 than in 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, 1.8–8.0), compared to PH-BPD infants without an atrial shunt.

* Corresponding author. Department of Pediatrics, Seoul National University Children's Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-769, South Korea.
E-mail address: kimhans@snu.ac.kr (H.-S. Kim).
[†] These two authors contributed equally to this work.

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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 a more tailored prognostic evaluation and treatment are recommended.

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 reports 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 such as long hospitalizations and oxygen therapy.[3–5]

The pathogenesis of PH in infants with BPD is multifactorial, and infants with BPD may develop PH because of 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] 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 may be at an increased risk for PH.[9,10] It maybe that even minor increases in left-to-right shunting of the blood through atrial defects may 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.

2. Materials and methods

This study was approved by the Institutional Research Ethics Committee at Seoul National University Hospital (Seoul, South Korea).

2.1. 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 (Seoul, South Korea) between January 2005 and March 2013. During the study period, 383 preterm infants were diagnosed as having BPD. Excluded from the study were infants with major congenital heart diseases [except for patent ductus arteriosus (PDA)], patent foramen ovale (PFO), and atrial septal defect (ASD)], chromosomal abnormalities, congenital diaphragmatic hernia, and persistent PH. 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. Patients with PDA that were treated with cyclooxygenase inhibitors or surgical ligation and hemodynamically significant residual PDAs after 36 weeks PMA were excluded. Bronchopulmonary dysplasia was defined using the National Institute of Child Health criteria and was graded as "mild", "moderate", or "severe", according to the fraction of inspired oxygen (FiO_2) or use of positive pressure ventilation (PPV). "Mild BPD" was defined as breathing room air; "moderate BPD" was defined as a FiO2 $<$ 0.30, and "severe BPD" was defined as $FiO_2 \geq 0.30$ or use of PPV at 36 weeks PMA. A pediatric cardiologist at Seoul National University Children's Hospital reviewed serial echocardiographic data such as evaluations with two-dimensional, M-mode, and color-coded Doppler for all preterm infants with moderate to severe BPD. Infants were diagnosed with PH if an echocardiogram that was performed when they were older than 2 months demonstrated elevated pulmonary artery pressure, based on the presence of at least one of the following criteria: (1) velocity of tricuspid valve regurgitation (TR) $\geq$ 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 atrial shunts (ASD or PFO) that remained open at the corrected postnatal age of 2 months.[15]

2.2. 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-square test and the Fisher's exact test, and $p < 0.05$ were considered significant. The significant variables identified by univariate analysis were further assessed with multivariable logistic regression analysis. Data are presented by the mean ± the