Pulmonary Hypertension in Preterm Infants: Prevalence and Association with Bronchopulmonary Dysplasia

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Objective To determine whether early pulmonary hypertension (PH) at 10-14 days of life in preterm infants is associated with bronchopulmonary dysplasia (BPD) at 36 weeks' postmenstrual age (PMA).

Study design This was a prospective observational cohort study of infants <28 weeks' gestation. Exclusion criteria were any major anomaly, genetic syndrome, or death before the initial echocardiogram. Echocardiograms were performed between 10 and 14 days of life and at 36 weeks' PMA to assess PH. BPD and its severity were determined at 36 weeks PMA by the National Institutes of Health workshop definition.

Results From March 2011 to April 2013, of 146 consecutively admitted infants <28 weeks, 120 were enrolled. One infant was excluded, 17 did not consent, and 8 died before undergoing a study echocardiogram. At 10-14 days of life, 10 infants had early PH (8%). Male sex (56% vs 40%), gestational age ($26^{+2} \pm 1^{+2}$ vs $25^{+6} \pm 1^{+4}$ weeks), birth weight (837 ± 205 g vs 763 ± 182 g), and small for gestational age (14% vs 20%) were not significantly different among infants with no PH and early PH, respectively. Infants with early PH required >0.3 fraction of inspired oxygen by day 10 of life (70% vs 27%, $P < .01$). Moderate/severe BPD or death was greater among infants with early PH (90%) compared with no PH (47%, relative risk 1.9, 95% CI 1.43-2.53).

Conclusion In this prospective, single-center cohort, early PH was associated with moderate/severe BPD or death at 36 weeks' PMA. *(J Pediatr 2014;165:909-14)*.

Bronchopulmonary dysplasia (BPD) is the most common complication of prematurity, affecting more than 10 000 infants per year in the US.[1] Despite recent advances in neonatal care, the incidence of BPD has increased[2]; however, the "new BPD" differs from the BPD first described in 1967 by Northway et al.[3] Rather than fibrosis and scarring of the lungs, the new BPD is characterized by alveolar simplification and pulmonary vascular hypoplasia or dysplasia.[4,5]

The risk factors for BPD include mechanical ventilation, oxygen toxicity, inflammation, and pulmonary edema caused by fluid overload or excessive left to right shunting; however, preterm infants without such risk factors can still develop BPD.[6-8] There is a complex crosstalk between pulmonary alveolar and vascular development.[9] A number of studies have found an association between pulmonary hypertension (PH) and respiratory distress syndrome (RDS)[10] or BPD.[11]

Among infants with BPD, PH has been a well-recognized association or complication.[12] In a retrospective study of infants with BPD, no risk factor for PH associated with BPD was identified on multivariate analysis; however, the role of early PH was not assessed.[13] PH frequently is associated with severe RDS.[14] Subhedar and Shaw[15] reported that pulmonary artery pressure (PAP) remained elevated up to 1 year of age among infants with chronic lung disease. These observations raise the possibility that PH that occurs in association with severe RDS may not resolve in infants who develop BPD and may persist for years.

The role of early PH as a risk factor for BPD and late-onset PH among extremely premature infants remains unclear. We conducted a prospective, single-center cohort study to examine the association of early PH with moderate/severe BPD and late-onset PH or death at 36 weeks' postmenstrual age (PMA). We hypothesized that echocardiographic evidence of early PH (PH between 10 and 14 days of life) is associated with moderate or severe BPD or death at 36 weeks' PMA. Our secondary hypothesis was that early PH is associated with late PH or death at 36 weeks' PMA.

Methods

This was a prospective, observational cohort study of preterm infants (<28 weeks' gestation based on obstetric criteria) admitted to the neonatal intensive care unit (NICU) of Women & Infants

BPD	Bronchopulmonary dysplasia	RDS	Respiratory distress syndrome
FiO_2	Fraction of inspired oxygen	RR	Relative risk
NICU	Neonatal intensive care unit	sBP	Systolic blood pressure
PAP	Pulmonary artery pressure	sPAP	Systolic pulmonary artery pressure
PDA	Patent ductus arteriosus	SpO_2	Pulse oximetry
PH	Pulmonary hypertension	TR	Tricuspid regurgitation
PMA	Postmenstrual age	VSD	Ventricular septal defect

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Hospital of Rhode Island. With Institutional Review Board approval and parental consent, infants were enrolled before 14 days of life. We excluded infants with congenital heart disease (except patent ductus arteriosus [PDA], small ventricular septal defect [VSD], atrial septal defect, or patent foramen ovale), congenital pulmonary anomaly (cystic adenomatoid malformation, lobar emphysema, etc), congenital diaphragmatic hernia, or death before the first study echocardiogram.

All infants were managed by the clinical teams in the NICU according to the local guidelines. Clinical teams targeted an oxygen saturation (SpO_2) as close to 90% as possible (lower and upper alarm limits of 85% and 95%, respectively) and fraction of inspired oxygen (FiO_2) was adjusted by the nurses. Study echocardiograms were performed with real-time pulse oximetry. Initial minimum and maximum SpO_2, along with the respective FiO_2 values, were recorded during echocardiography; however, SpO_2 and FiO_2 data were not collected for clinical echocardiograms. If echocardiography was performed for clinical indications, a study echocardiogram was not performed, and data were obtained from clinical studies. All study echocardiograms were performed by a pediatric echocardiography technician, a NICU fellow (trained under the supervision of a pediatric cardiologist), or either of the 2 pediatric cardiologists (J.Z., S.F.) on the study team. In addition, both pediatric cardiologists were blinded to the clinical status of each infant and either one reviewed each echocardiogram for the presence and severity of PH. Management in the NICU was otherwise according to the discretion of the clinical care teams responsible for the infant.

Right ventricular pressure gradient was estimated by measuring the peak velocity of tricuspid regurgitation (TR max) if there were reproducible holosystolic envelopes. We used the modified Bernoulli equation to convert Doppler derived velocity to pressure (pressure gradient between right ventricle and right atrium = $4 \times [TR\ max^2]$). Systolic PAP (sPAP) was calculated by adding right atrial pressure (5 mm Hg) to estimated right ventricle pressure gradient. In the absence of measureable TR, we relied upon a PDA or VSD gradient to estimate sPAP and identify the severity of PH as described previously. The severity of PH was determined by comparing simultaneously estimated sPAP with systemic systolic blood pressure (sBP).

PH was categorized as none or mild if the estimated sPAP to sBP ratio was <0.5, moderate if the pulmonary to systemic systolic ratio was ≥0.5 but <1, and severe or suprasystemic if sPAP ≥ sBP.[16] In the absence of TR, PDA, or VSD, sPAP was estimated by assessing the end-systolic interventricular septal position at the papillary muscle level in short-axis view through the multiple acoustic windows. PH by septal position was categorized as follows: normal or mild if the septum was rounded at end systole, moderate if the septum was flattened, and suprasystemic if the septum was bowed into the left ventricle at end systole.[11]

Infants with moderate or severe PH on the initial echocardiogram (10-14 days of life) were classified as having early PH. Infants with mild or no PH on the initial echocardiogram were identified as no PH group. For the purpose of this study, PH identified by echocardiogram at 36 weeks' PMA has been described as late PH. Study echocardiogram findings, which were deemed noncritical to the clinical care of infants, were not conveyed to the family or the clinical teams. Potentially important echocardiographic findings (eg, severe PH, hemodynamically significant PDA, hypertrophic cardiomyopathy with dynamic left ventricular outflow tract obstruction, or cardiac valvular lesions) were revealed to the clinical team. Clinical management of divulged echocardiographic findings was at the discretion of providers in the NICU.

BPD was diagnosed if an infant received supplemental oxygen for ≥28 days. BPD was classified into mild, moderate, or severe forms at 36 weeks' PMA, as described by Jobe and Bancalari.[17] Mild BPD was the absence of supplemental oxygen, moderate BPD was the need for <0.3 FiO_2, and severe BPD was the use of positive pressure ventilation or need for >0.3 FiO_2. The need for continuing oxygen therapy was determined by an O_2/room air challenge reduction as outlined by Walsh et al.[18]

We calculated sample size using the incidence of moderate or severe BPD at Women & Infants Hospital in 2006 (34%) and an estimated frequency of early PH (15%). To detect a 30% increase in moderate/severe BPD secondary to early PH, 120 infants were required, using a power of 80% and an alpha of 0.05. Maternal, perinatal, and neonatal data were collected to characterize the demographic and clinical characteristics of the study cohort. Infants were dichotomized based on the presence or absence of early PH at 10-14 days of life. χ^2 tests were used for categorical variables, and Student t tests were used to compare continuous variables for infants with and without early PH. Bivariate analysis was performed to identify associations between early PH and study outcomes of BPD or late PH at 36 weeks' PMA. Associations between early PH and BPD or late PH were expressed as a relative risk (RR) with 95% CI.

Results

Between March 2011 to April 2013, 146 infants of <28 weeks' gestation were admitted to the NICU at Women & Infants Hospital of Rhode Island, and 120 were enrolled. Consent was declined for 17 infants, and 8 died before undergoing the initial study echocardiogram. Only 1 infant was excluded because of vertebral and chest wall anomalies.

The initial echocardiography on 12 ± 2 days of life indicated the presence of PH (early PH) in 10 infants (8%) and 110 had no PH. All infants with early PH had moderate PH. The diagnosis of early PH (n = 10) was based on TR in 2 infants, a PDA gradient in 5, and septal position in 3 infants. Because PH had not been diagnosed clinically, specific treatment for PH was not administered to these infants. Three infants, previously treated with inhaled nitric oxide during their first week of life because of persistent PH, were not receiving inhaled nitric oxide at the time of initial study echocardiogram; only 1 of those 3 infants with persistent PH had early PH diagnosed on day 14 of life. Maternal