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ORIGINAL ARTICLE

Echocardiographic detection of pulmonary hypertension in extremely low birth weight infants with bronchopulmonary dysplasia requiring prolonged positive pressure ventilation

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Objective: The goal of this study was to delineate the epidemiology of echocardiographically diagnosed pulmonary hypertension (PH) in extremely low birth weight (ELBW) infants with bronchopulmonary dysplasia (BPD) requiring prolonged positive pressure ventilation (PPV), and to determine the independent relationship between PH and mortality in these patients.

Study Design: Our retrospective cohort included ELBW infants, with BPD requiring prolonged PPV, hospitalized in Cincinnati, Ohio during 2003–2009, as recorded in the National Institute of Child Health and Human Development Neonatal Research Network Database. Following chart review, a logistic regression model was constructed to understand the contribution of PH to mortality in infants with BPD requiring prolonged PPV.

Result: We identified 216 patients (19%) with BPD requiring prolonged PPV among 1156 ELBW infants. Of these patients, 41% received echocardiography after 4 weeks of life, with 37% showing evidence of PH. Logistic regression analysis demonstrated that infants with BPD requiring prolonged PPV, with PH detectable by echocardiogram, were four times more likely to die (adjusted odds ratio): 4.6, 95% confidence interval: 1.3–16.5) when compared with infants with BPD requiring prolonged PPV without echocardiographic evidence of PH.

Conclusion: Pulmonary hypertension appears to be an important, independent determinant of death in infants with BPD requiring prolonged PPV.
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Keywords: pulmonary hypertension; bronchopulmonary dysplasia; echocardiogram; extremely low birth weight infant; neonatal

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Introduction

Innovations in neonatal care have led to increased survival rates for extremely low birth weight (ELBW) infants (birth weight <1000 g). As survival improves, morbidities among survivors have changed.[1] Even though bronchopulmonary dysplasia (BPD) is the most common complication among premature infants, advances in neonatal care that include antenatal glucocorticoids, surfactant treatment and gentle ventilation strategies have changed the pathological features and clinical course of BPD. Historically, oxygen toxicity and ventilator-induced injury, resulting in inflammation, fibrosis and smooth muscle hypertrophy in the airways characterized BPD in premature infants.[2] In the surfactant era, the pathology of BPD is likely due to disruption in the normal sequence of lung development in ELBW infants.[3] This 'new' BPD is characterized by decreased numbers and volume of alveoli, and deficiencies in the number and size of intra-acinar pulmonary arteries. These changes are responsible for a significant reduction in the total cross-sectional area of the pulmonary vascular bed.[4] This reduction in the vascular cross-sectional area and alveolar hypoxia results in structural remodeling of the pulmonary vasculature, abnormal vasoreactivity and subsequent development of pulmonary hypertension (PH).[3,4]

Although the mechanisms responsible for elevated pulmonary vascular resistance and altered reactivity remain incompletely understood, the development of PH is a recognized and sometimes serious complication of severe BPD that can contribute significantly to the morbidity and mortality rates of preterm infants.[4,5] Persistent echocardiographic evidence of PH beyond the first few months of life has been associated with up to 40% mortality in infants with BPD.[6] However, the true prevalence of PH in BPD and the rate of BPD mortality attributable to PH are unknown.[7] Diagnosis of pulmonary vascular disease in this population is difficult and requires a high degree of suspicion because the symptoms of PH may be subtle and masked by the signs of BPD itself, even in patients with significantly elevated pulmonary artery pressures.[8]

Epidemiological research of PH is increasingly needed, as the rate of BPD in the ELBW population has stabilized[2,9,10] and clinical

attention has become increasingly focused upon the late-pulmonary outcomes of BPD survivors.[11] If PH were found to be highly prevalent and associated with increased mortality in ELBW infants with severe cases of BPD, closer echocardiographic surveillance for PH might be warranted. Early detection of PH by echocardiogram could prompt more thorough diagnostic testing via cardiac catheterization and provide prognostic information to influence the use of targeted interventions such as vasodilator therapies.[8] Patients with documented PH might also benefit both from increased monitoring during periods of perioperative stress and acute illness, and from closer follow-up upon discharge.

Our objectives were to delineate the epidemiology of echocardiographically diagnosed PH in ELBW infants with BPD requiring prolonged positive pressure ventilation (PPV), including the determination of the minimum prevalence of PH in our cohort, and to test the hypothesis that PH is an important determinant of death in ELBW infants with BPD requiring prolonged PPV.

Methods

Subjects and definitions

The National Institute of Child Health and Human Development Neonatal Research Network Database was utilized to identify ELBW infants with BPD requiring PPV at 28 days of age who were born during 2003–2009, and cared for in any of three Level III Neonatal Intensive Care Units (Cincinnati Children's Hospital Medical Center, Good Samaritan Hospital, University of Cincinnati Hospital) that serve the tri-state region of Northern Kentucky, South-eastern Indiana and South-western Ohio. During the study period, these hospitals served as the tertiary care referral centers for all infants born at a gestational age of <32 weeks within the tri-state region.

Bronchopulmonary dysplasia was defined as receiving supplemental oxygen at 36 weeks post-menstrual age. Infants with BPD were defined as requiring prolonged PPV if they were on continued respiratory support at 28 days post-natal age by one of the following modalities: mechanical ventilation, continuous positive airway pressure (CPAP) or nasal cannula flow $>2\,l\,min^{-1}$. Infants were considered to have PH if an echocardiogram was performed after 30 days post-natal age that demonstrated elevated pulmonary artery pressure (pulmonary artery pressure $>50\%$ systemic or evidence of right ventricular failure consistent with PH) as determined by a pediatric cardiologist at Cincinnati Children's Hospital Medical Center. Presence of right ventricular hypertrophy, tricuspid regurgitation jet, right to left shunt and/or septal flattening were recorded when present in the setting of PH. Infants with known structural lung, airway, pulmonary vascular or major cardiac anomalies at birth were excluded. The overall outcome was death due to any reason during the neonatal intensive care unit stay in the cohort of ELBW infants with BPD requiring prolonged PPV.

This study was approved by the institutional review boards of Cincinnati Children's Hospital Medical Center, the Good Samaritan Hospital of Cincinnati and the University of Cincinnati. Waivers of informed consent were granted from each institution.

Data sources

Data were obtained from two sources, the National Institute of Child Health and Human Development Neonatal Network Database and chart review. The National Institute of Child Health and Human Development Neonatal Network Database is a registry of very low birth weight infants (birth weight <1500 g), who were born between 22 0/7 and 28 6/7 weeks (<29 weeks), inclusive gestational age, and/or between 401 and 1500 g, inclusive birth weight. Infants qualified for inclusion in the very low birth weight registry when they were admitted to a network center within 14 days of birth or were live-born, but died in the delivery room. Research nurses collected demographic, perinatal and infant data at each participating center using common definitions developed by investigators and described in previous publications.[12,13]

Cincinnati Children's Hospital Medical Center, the University of Cincinnati Hospital and Good Samaritan Hospital are participating centers in the database. Records were reviewed from these three institutions to identify all ELBW infants (birth weight <1000 g) in the tri-state region during 2003–2009 with BPD and PPV at 28 days of age. Infant demographic information extracted included birth weight, gestational age, surfactant administration, patent ductus arteriosus (PDA) and its treatment, duration of mechanical ventilation, diuretic usage, intraventricular hemorrhage and its grade, necrotizing enterocolitis (NEC) and its severity, any surgical procedures and late-onset sepsis.

Patients that met our inclusion requirements were linked to identifiers for chart review at the respective hospitals. The chart review was conducted to collect information regarding echocardiographic results, treatment for PH and autopsy results. Echocardiograms were ordered at physician discretion as clinically warranted, and may or may not have been obtained with the goal of assessing for PH. Treatment for PH was defined as the use of nitric oxide and/or sildenafil at greater than 2 months of age. All autopsy results were reviewed when available.

Database variables

Antenatal steroids were defined as administration of any corticosteroid to accelerate fetal lung maturity in the concurrent pregnancy. Estimated gestational age, in completed weeks, was determined by best obstetric estimate using last menstrual period, standard obstetric parameters and ultrasonography. When there was a 2-week range of gestational age among obstetric estimates, the lowest estimate was used. When there was a 3-week range of several existing estimates, the median gestational age estimate was used. Data were also collected on diagnoses (including PDA), treatments, and in-hospital morbidities until death, discharge or

120 days; after 120 days or if the patient was transferred, then data were collected regarding death or discharge to home. Surfactant treatment was defined as one or more doses of any surfactant during hospitalization. Intraventricular hemorrhage was reported according to the classification of Papile *et al*.[14] Late-onset sepsis was defined as a positive blood or cerebral spinal fluid culture obtained in the presence of compatible clinical signs of septicemia occurring after 72 h of age. Data regarding NEC were collected for infants who survived >12 h and was defined as modified Bell's classification stage IIA or greater.[15] Surgery for NEC was at the discretion of each individual network center and included any surgical intervention (drain, laparotomy or both).

Statistical analysis

SAS V9.2 (Cary, NC, USA) was used to analyze the data. Unadjusted (crude) associations between group status for the hypothesis (PH vs no PH) and neonatal characteristics were explored through bivariable analysis using χ^2, Fisher's exact, Wilcoxon or *T*-test where appropriate. A multiple logistic regression model was constructed for our hypothesis to understand the independent relationship between PH and death while controlling for other covariates and confounders. A stepwise approach was taken to determine which variables remained in the final multivariable model. Variables were included in the regression models that were found to be significantly related to the outcome at the $P<0.05$ level in unadjusted analysis and remained in the final model if they were significant at $P<0.05$. The Hosmer–Lemeshow test was conducted to determine the model's goodness of fit.

Results

A total of 1156 ELBW infants were evaluated (Figure 1), with 341 (29.4%) having BPD. Out of these, 216 infants with BPD required prolonged PPV, defined as ventilation, CPAP, or >21 nasal cannula flow at >28 days of life. Overall, 16 infants were excluded due to known structural lung, airway or major cardiac anomalies at birth. Additionally, 10 infants were excluded because their medical records could not be traced. All 190 included infants met the conventional criteria for BPD, oxygen requirement at 28 days of life and the NIH consensus definition of severe BPD.[2] Of patients with BPD on prolonged PPV that met inclusion criteria, 78/190 (41%) had echocardiography after 4 weeks of life, with 29/78 (37%) showing evidence of PH. There was a 2.8-fold increase (unadjusted odds ratio) in mortality in infants with BPD requiring prolonged PPV when PH was present (38 vs 14%).

Clinical characteristics of all infants with BPD requiring prolonged PPV are summarized in Table 1 by echocardiogram status. Infants with a lower birth weight and longer duration of respiratory support (mechanical ventilation, CPAP or oxygen therapy) were more likely to undergo echocardiography after 30 days of life. In addition, infants who had an echocardiogram

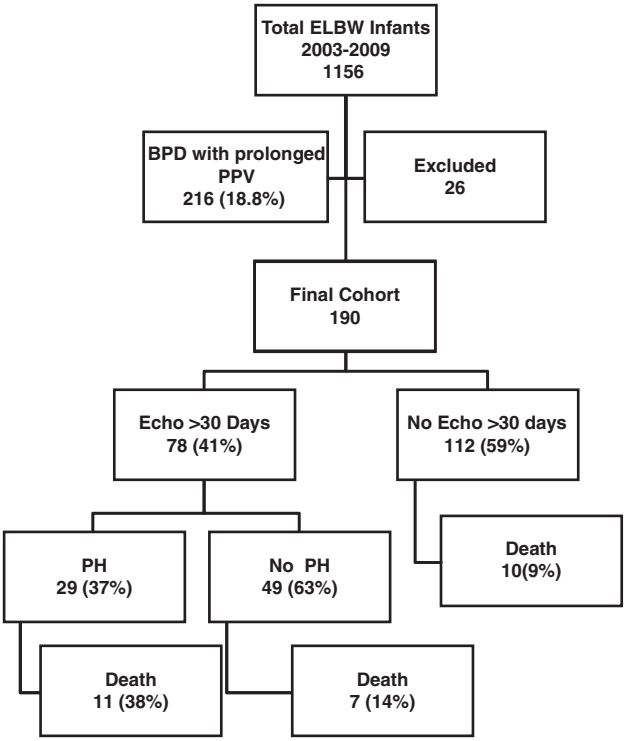

Figure 1 Flow of extremely low birth weight infants (<1000 g) from inclusion into the cohort of infants with bronchopulmonary dysplasia on prolonged positive pressure ventilation to the measured outcome: survival vs death.

were more likely to have persistent patency of the ductus arteriosus. Gender, race, oxygen status at discharge, surgery for PDA and incidence of NEC were not different between those who did and those did not have an echocardiogram performed. However, infants who had an echocardiogram had a significantly higher incidence of death.

Among infants with BPD requiring prolonged PPV who had an echocardiogram, birth weight, gestational age, gender, race, incidence of major complications during the neonatal intensive care unit stay (NEC, surgery for PDA) and duration of mechanical ventilation were not different between those with and those without PH. Infants with PH spent less days on average on CPAP when compared with infants without PH (Table 2). The unadjusted incidence of death was greater in the PH group.

Multiple logistic regression modeling demonstrated that infants with BPD requiring prolonged PPV who developed PH were more likely to die (adjusted odds ratio: 4.6, 95% confidence interval: 1.3–16.5) when compared with infants with BPD requiring prolonged PPV who did not develop PH after controlling for NEC, sepsis, severe intraventricular hemorrhage, birth weight and PDA (Table 3) (Hosmer–Lemeshow test, $P=0.14$).

Autopsy results were only available for 6 of the 28 ELBW infants with BPD requiring prolonged PPV that died. One infant had evidence of BPD with severe PH, right ventricular hypertrophy and hepatosplenomegaly.

Table 1 Characteristics of extremely low birth weight infants with bronchopulmonary dysplasia on prolonged positive pressure ventilation ($N = 190$)

Characteristics	*No echo* (N = *112*)	*Echo* (N = *78*)	P-*value*
Birth weight[a]	779 ± 122	734 ± 133	0.016[b]
Gestational age[a]	25 ± 1.3	25 ± 1.5	0.006[c]
Female, *n* (%)	58 (52)	36 (46)	0.409
Caucasian, *n* (%)	32 (29)	18 (23)	0.398
Antenatal antibiotics, *n* (%)	65 (58)	51 (65)	0.343
Antenatal steroids, *n* (%)	92 (82)	67 (86)	0.577
Surfactant, *n* (%)	85 (76)	64 (82)	0.470
PDA>30 days, *n* (%)	13 (12)	40 (51)	<0.0001
Surgery for PDA, *n* (%)	13 (12)	15 (19)	0.704
NEC, *n* (%)	17 (15)	18 (23)	0.167
Severe IVH, *n* (%)	2 (2)	10 (13)	0.004[d]
Discharged home on oxygen, *n* (%)	32 (29)	20 (26)	0.147
Death, *n* (%)	10 (9)	18 (23)	0.006
Days on oxygen[a]	81 ± 35	113 ± 62	<0.0001[c]
Days on mechanical ventilation[a]	20 ± 19.7	39 ± 21.9	<0.0001[c]
Days on CPAP[a]	25 ± 17.5	15 ± 16.8	<0.0001[c]

Abbreviations: CPAP, continuous positive pressure ventilation; Echo, echocardiogram; intraventricular hemorrhage, IVH; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus.
[a]Mean ± s.d.
χ^2-test used for statistical analysis unless otherwise noted:
[b]*T*-test.
[c]Wilcoxon analysis.
[d]Fischer's Exact—two-sided probability.

Five patients (17%) who were diagnosed with PH by echocardiogram at >30 days of age, received vasodilator therapy. All were treated with nitric oxide. In addition, three also received sildenafil. No patients were treated with sildenafil in isolation. Despite intervention, all five patients whose PH was treated with vasodilators died.

Discussion

When we retrospectively used the results of echocardiograms obtained at greater than 30 days of age in our regional cohort of ELBW infants with BPD requiring prolonged PPV, PH was detected in 37%. This demonstrated that, at a minimum, 15% (29/190) of our total population of ELBW infants with BPD requiring prolonged PPV with ventilation, CPAP or >2 l nasal cannula flow at 28 days of life suffered from co-existing PH. When confounders were controlled for, the presence of PH on echocardiogram led to a nearly fivefold increase in the odds of death. These findings indicate that PH is prevalent within the subsection of the ELBW population with BPD on prolonged PPV, and that it appears to be an important risk factor for death in these infants.

Previous research has shown that PH develops in some infants with BPD and that it can contribute to BPD-associated morbidity and mortality.[4,5] However, there is a paucity of evidence regarding appropriate clinical surveillance for PH in BPD patients, and the prevalence of PH in these infants remains unknown.[5,7,16]

Very few studies have estimated the minimum prevalence of PH within a population of patients with BPD.[7,16] An *et al*.[7] recently used echocardiograms to evaluate a group of 116 very low birth weight infants and observed a 25% prevalence of PH in patients with BPD. However, their study differed from ours in that the BPD severity within their cohort ranged from mild (breathing room air) to severe, and birth weights ranged from 430 to 1560 g.[7] We

Table 2 Characteristics of the infants who received an echocardiogram after 30 days of life according to pulmonary hypertension status ($N = 78$)

Characteristics	*No PH* (N = *49*)	*PH* (N = *29*)	P-*value*
Birth weight[a]	733 ± 144.19	735 ± 114.93	0.959[b]
Gestational age[a]	25 ± 1.43	25 ± 1.50	0.801[c]
Female, *n* (%)	21 (43)	15 (52)	0.448
Caucasian, *n* (%)	11 (22)	7 (24)	0.864
Antenatal antibiotics, *n* (%)	33 (67)	18 (62)	0.636
Antenatal steroids, *n* (%)	46 (94)	21 (72)	0.058
Surfactant, *n* (%)	38 (78)	26 (90)	0.231
PDA>30 days, *n* (%)	23 (47)	17 (59)	0.281
Surgery for PDA, *n* (%)	10 (20)	5 (17)	0.695
NEC, *n* (%)	12 (24)	6 (21)	0.700
Severe IVH, *n* (%)	5 (10)	5 (17)	0.369
Death, *n* (%)	7 (14)	11 (38)	0.019
Discharged home on oxygen, *n* (%)	13 (27)	7 (24)	0.633
Days on oxygen[a]	113 ± 66.56	113 ± 56.00	0.610[c]
Days on mechanical ventilation[a]	36 ± 22.30	42.69 ± 21.20	0.257[c]
Days on CPAP[a]	19 ± 17.58	8.07 ± 12.50	0.003[c]

Abbreviations: CPAP, continuous positive airway pressure; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PH, pulmonary hypertension.
[a]Mean ± s.d.
χ^2-test used for statistical analysis unless otherwise noted:
[b]*T*-test.
[c]Wilcoxon analysis.

Table 3 Adjusted odds ratios and 95% confidence intervals for death vs covariates in multivariate logistic regression

Risk factor	*PH vs no PH*[a] *adjusted OR (95% CI)*
Pulmonary hypertension	4.6 (1.3–16.5)
Birth weight	0.9 (0.9–1)
Necrotizing enterocolitis	1.3 (0.3–5.4)
Sepsis	1.3 (0.4–4.4)
Patent ductus arteriosus	0.4 (0.1–1.4)
Severe intraventricular hemorrhage	3.1 (0.5–17.5)

Abbreviations: CI, confidence interval; OR, odds ratio; PH, pulmonary hypertension.
[a]Model comparing infants with echocardiographic evidence of pulmonary hypertension with infants with no echocardiographic evidence of pulmonary hypertension.

restricted our cohort to ELBW infants with BPD that required prolonged PPV, because these infants on considerable respiratory support at 28 days of life are at the highest risk of developing PH because of a striking decrease in normal alveolar septation and microvascular development.[17,18] To our knowledge, our investigation was the first to review echocardiogram results to determine the minimum frequency of PH within a multi-year, regional cohort of ELBW infants with BPD requiring prolonged PPV, and to directly investigate the independent relationship between PH and death in this highly vulnerable population. An absolute frequency cannot be determined because only 41% of these infants underwent echocardiography.

In our study, infants with PH were less likely to have received antenatal steroids. Antenatal steroids may have a vital role in the regulation of vascular endothelial growth factor receptors that are instrumental in pulmonary angiogenesis and lung growth through nitric oxide-dependent mechanisms.[19,20] Disruption of vascular endothelial growth factor signaling because of premature birth impairs lung growth and sets the stage for late PH.[19–21] Lack of antenatal steroids has also been associated with decreased likelihood of closure of the ductus arteriosus.[22] Although not statistically significant, infants with PH in our study were also more likely to have a prolonged PDA. Prolonged PDA has been associated with BPD and PH.[23] Physiologically, PH may be a protective mechanism in neonates with prolonged PDA to prevent pulmonary overcirculation and consequent congestive heart failure. The relationship between the lack of antenatal steroids, prolonged PDA and PH in premature infants needs to be studied.

Echocardiograms, commonly available and non-invasive, are limited in their ability to differentiate severity of PH as compared with the gold standard of cardiac catheterization.[5,8] Despite this limitation, they are still considered the best method to screen BPD patients for PH at the population level[18] and often correctly identify infants with PH.[8,24] Recent technological advances such as myocardial tissue Doppler might increase the sensitivity of this important tool.[25]

The retrospective nature of our study imposed several limitations. As the use of echocardiography was selective, we were only able to determine a minimal estimate of PH in ELBW with BPD requiring prolonged PPV. It was also impossible for us to determine the efficacy of vasodilators in these patients. All of the patients in our cohort who had their PH treated with the vasodilators, sildenafil and nitric oxide, died. However, our chart review indicated that vasodilators were usually started only in those patients with the most severe clinical courses. Experience with PH therapies, such as intravenous epoprostenol, endothelin receptor blockers, aerosolized prostacyclin analogues, inhaled nitric oxide, sildenafil and other agents, is limited in the population of BPD patients.[26,27] Moreover, the long-term consequences of these potential therapies are unknown. Even though it is likely that echocardiograms tend to be ordered on the sickest infants, PH remains an important contributor to mortality even after controlling for the most prevalent causes of death in the neonatal intensive care unit.

In conclusion, our findings indicate that PH is prevalent and an important determinant of mortality in the ELBW population with BPD requiring prolonged PPV, and that it appears to be an important and overlooked risk factor for death in these highly vulnerable infants. Utilization of echocardiography as a surveillance tool for PH in infants with BPD, as suggested by experts in the field[28,29] may increase the likelihood of early PH diagnosis. Prospective studies of PH prevalence and treatment in BPD patients are needed to develop a screening strategy for PH in this high-risk group.

Conflict of interest

The authors declare no conflict of interest.

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