Early Pulmonary Vascular Disease in Preterm Infants Is Associated with Late Respiratory Outcomes in Childhood

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Abstract

Rationale: Early pulmonary vascular disease (PVD) after preterm birth is associated with a high risk for developing bronchopulmonary dysplasia (BPD), but its relationship with late respiratory outcomes during early childhood remains uncertain.

Objectives: To determine whether PVD at 7 days after preterm birth is associated with late respiratory disease (LRD) during early childhood.

Methods: This was a prospective study of preterm infants born before 34 weeks postmenstrual age (PMA). Echocardiograms were performed at 7 days and 36 weeks PMA. Prenatal and early postnatal factors and postdischarge follow-up survey data obtained at 6, 12, 18, and 24 months of age were analyzed in logistic regression models to identify early risk factors for LRD, defined as a physician diagnosis of asthma, reactive airways disease, BPD exacerbation, bronchiolitis, or pneumonia, or a respiratory-related hospitalization during follow-up.

Measurements and Main Results: Of the 221 subjects (median, 27 wk PMA; interquartile range, 25–28 and 920 g; interquartile range, 770–1090 g) completing follow-up, 61% met LRD criteria. Gestational diabetes and both mechanical ventilator support and PVD at 7 days were associated with LRD. The combination of PVD and mechanical ventilator support at 7 days was among the strongest prognosticators of LRD (odds ratio, 8.1; confidence interval, 3.1–21.9; $P < 0.001$). Modeled prenatal and early postnatal factors accurately informed LRD (area under the curve, 0.764). Adding BPD status at 36 weeks PMA to the model did not change the accuracy (area under the curve, 0.771).

Conclusions: Early echocardiographic evidence of PVD after preterm birth in combination with other perinatal factors is a strong risk factor for LRD, suggesting that early PVD may contribute to the pathobiology of BPD.

Keywords: late respiratory outcomes; echocardiography; prematurity; pulmonary vascular disease; mechanical ventilation

Bronchopulmonary dysplasia (BPD), the chronic lung disease that follows premature birth, remains a major cause of morbidity and mortality. BPD is characterized by an arrest of vascular and alveolar growth and

high risk for pulmonary hypertension (PH), yet mechanisms contributing to its pathogenesis and early strategies to prevent BPD are poorly understood (1). Infants with BPD are at risk for persistent late

respiratory morbidities, including prolonged need for supplemental oxygen, pulmonary vascular disease (PVD), recurrent acute respiratory exacerbations with frequent emergency room visits and

(Received in original form March 6, 2018; accepted in final form October 9, 2018)

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†S.H.A. is Associate Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

Supported by NIH/National Center for Research Resources (K23RR021921), NIH/NHLBI (R01 HL085703), and NIH/National Center for Advancing Translational Sciences Colorado Clinical Translational Sciences Institute (UL1 TR000154).

Author Contributions: Conception and design, P.M.M., E.W.M., A.Y., B.B.P., B.D.W., and S.H.A. Acquisition of data, P.M.M., A.Y., B.B.P., and S.H.A. Performed the analysis, P.M.M., M.M., J.T.B., and B.D.W. Drafting the manuscript for important intellectual content, P.M.M., E.W.M., M.M., J.T.B., S.A., B.D.W., and S.H.A. Review and revision of manuscript, all authors.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 199, Iss 8, pp 1020–1027, Apr 15, 2019

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Originally Published in Press as DOI: 10.1164/rccm.201803-0428OC on October 10, 2018

Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the

Subject: Early pulmonary vascular disease after preterm birth is associated with a high risk for developing bronchopulmonary dysplasia, but its relationship with late respiratory outcomes during early childhood remains uncertain.

What This Study Adds to the

Field: Early echocardiographic evidence of pulmonary vascular disease after preterm birth in combination with other perinatal factors is a strong risk factor for late respiratory disease, suggesting that early pulmonary vascular disease may contribute to the pathobiology of bronchopulmonary dysplasia.

hospitalizations, exercise intolerance, and pulmonary function abnormalities that can extend into adulthood (1–3). Preterm infants with and without BPD exhibit significant respiratory morbidity that extends well beyond the perinatal period. Rehospitalization is common among preterm infants during the first 2 years of life (4–7), with respiratory disease being the most common cause of readmission. Although BPD has been most closely associated with poor respiratory outcomes after discharge, it is becoming increasingly evident that preterm infants born at later gestational ages (GAs) and early preterm infants without the diagnosis of BPD have greater morbidity and mortality than term infants (8). Thus, controversies persist regarding how to best define BPD and whether having this diagnosis at 36 weeks postmenstrual age (PMA) adequately reflects the late risk for lung disease during childhood and into adult life (9).

A recent NHLBI-sponsored workshop highlighted the importance of prenatal and early postnatal exposures on postnatal lung growth and development, and its subsequent contribution to late respiratory function and disease throughout childhood (10). The pathophysiology of BPD is complex and may differ substantially depending on the prenatal and postnatal exposures (9). Past laboratory studies have shown that injury to the lung vasculature can disrupt angiogenesis, which directly

impairs alveolarization, supporting the hypothesis that endothelial–epithelial crosstalk plays a critical role during lung development, and that strategies that serve to preserve or enhance endothelial survival, growth, and function may improve lung vascular and alveolar growth in neonatal lung disease (the so-called “vascular hypothesis” of BPD) (11, 12). Previous studies suggest that early echocardiographic evidence of PVD in preterm neonates contributes to BPD and late PH (13, 14). However, whether evidence of early PVD is associated with respiratory outcomes during early childhood remains unknown.

We hypothesized that early evidence of PVD in infants born preterm would be an independent risk factor for late respiratory disease (LRD) during early childhood and would augment the accuracy of prediction models including other selected perinatal factors. To test this hypothesis, we conducted a prospective longitudinal study of preterm infants undergoing routine echocardiogram screening at 7 days of age and 36 weeks PMA at two academic medical centers who were serially followed with primary caregiver surveys at 6-month intervals through 2 years corrected age. Some of the results of this study have been previously reported in the form of an abstract (15).

Methods

Subjects were enrolled in a prospective, observational study at affiliated hospitals of two academic medical centers between July 2006 and March 2012. A detailed description of the cohort has been previously described (14). To summarize, preterm infants without congenital cardiopulmonary abnormalities and anticipated to survive to discharge who were born less than 34 weeks GA with birthweights between 500 and 1,250 g were enrolled within 7 days of birth. Children who transferred, withdrew from the study, or died before 36 weeks PMA assessments could be collected were excluded from analysis. Written parental consent was obtained for all participants following institutional review board approval of the protocol at each of the institutions.

Demographics, prenatal, and postnatal information were collected to discharge, transfer to a nonstudy hospital, or death. Maternal smoking status was assessed

through self-identification at the initial subject assessment. Birthweight z-scores were calculated using data provided from Oken and colleagues (16). Infants were considered small for GA if the birth weight z-score was below the 10th percentile for sex and GA. Other definitions of subject characteristics are provided in Table E1 in the online supplement. Echocardiograms were performed at 7 days of age and at 36 weeks PMA, which were interpreted by a single cardiologist (A.Y.) who was blinded to the subjects’ clinical status. Patients were diagnosed with early PVD if they met one or more of the following criteria on the echocardiogram performed at 7 days of age: systolic pulmonary artery pressure greater than 40 mm Hg by tricuspid jet velocity, pulmonary artery pressure/systemic systolic pressure greater than 0.5, cardiac shunt with bidirectional or right-to-left flow, or any degree of septal wall flattening. We used the term “PVD” (rather than PH) to describe these echocardiogram abnormalities because there is some controversy about the timing of changes in echocardiogram findings during the normal transition from the fetal to postnatal circulation.

Thus, these early echocardiogram criteria reflect elevated pulmonary artery pressure but are not necessarily indicative of sufficient PH to impair oxygenation because of extrapulmonary right-to-left shunt or cause right ventricular dysfunction in preterm infants, as observed in classic persistent PH of the newborn. There is strong consensus, however, that these echocardiographic abnormalities represent PH when measured at 36 weeks PMA (13, 14, 17). BPD severity, as based on standard NIH criteria as none, mild, moderate, and severe disease, was assessed at 36 weeks PMA through the application of an oxygen reduction test (18) and modification of the proposed NIH criteria (19) including adjustment for Denver’s altitude (1,600 m) as previously reported (14, 20).

Follow-up questionnaires were administered to primary caregivers either in person or via telephone at 6-month intervals during the first 2 years of life. If a survey time point was missed, the subsequent survey encompassed the period of time back to previous contact. Surveys included items regarding respiratory symptoms, visits to health care providers, hospital admissions, respiratory support and medications, and environmental exposures. A child was

considered to have LRD if he or she was diagnosed with asthma, reactive airways disease, a BPD exacerbation, bronchiolitis, or pneumonia by a physician or hospitalized for a respiratory illness during the first 2 years corrected age. Included subjects were required to have completed at least one survey. We allowed respondents to have incomplete information for no more than two specific survey questions (out of four) for data to be used to define LRD status.

Statistical Analysis

All data were collected and stored using a REDCap (Research Electronic Data Capture) database through the University of Colorado Denver Development and Informatics Service Center (21). Tests of association were computed for demographic and prenatal outcomes stratified by an overall respiratory diagnosis. Chi-square tests were used to compare categorical variables across the diagnosis status; Wilcoxon rank sum tests were used for comparison of continuous variables. Multivariable logistic regression modeled the odds of LRD as a function of

early (within 7 d after birth) clinical factors. Complete covariate information was required to estimate associations in the final analytic model selected. Potential covariates included maternal smoking; antenatal corticosteroids; preexisting diabetes; gestational diabetes; preeclampsia; prolonged rupture membranes; chorioamnionitis; antepartum hemorrhage; cesarean section; multiple gestation; sex; GA; birthweight z-score; small for GA; study site; individual assessments at 7 days of age including presence of ventilator support, PVD, patent ductus arteriosus, patent foramen ovale, ventricular septal defect, measurable tricuspid jet velocity, right atrial enlargement, right ventricular dilatation, and septal wall flattening; interaction between PVD at 7 days of age and BPD dichotomous diagnosis (none/mild or moderate/severe); interaction between PVD and ventilator support at 7 days of age; and PH at 36 weeks PMA. A stepwise model selection approach determined the most parsimonious model with a maximum of 12 clinical factors included as covariates.

Selection criteria used the score statistic to compare models.

For comparison, separate models were created from perinatal factors alone, perinatal factors plus BPD status (multilevel classification), and BPD status (multilevel classification) alone. Area under the curve (AUC) was determined and comparisons were made to examine the accuracy of these models to reflect the likelihood of LRD. The most parsimonious multivariable logistic regression model with LRD as the outcome was selected via a branch-and-bound algorithm of Furnival and Wilson (22) as based on the highest score statistic. Based on the event rate, the best model selected included 10 covariates (23, 24).

The number of covariates was selected based on the number of respiratory events (25). For comparison, another logistic regression was fit on LRD, with the multilevel BPD diagnosis as the only prognosticator. AUC from receiver operating characteristic curves was used to examine and compare the discriminatory accuracy of multiple models. Statistical significance level was set at alpha less than

Table 1. Subject Characteristics

	No Late Respiratory Disease (n = 86) [n (%) or Median (IQR)]	Late Respiratory Disease (n = 135) [n (%) or Median (IQR)]	P Value
Gestational age, wk	27 (26 to 29)	27 (25 to 28)	0.088
Birth weight, g	975.5 (788 to 1,128)	900 (765 to 1,075)	0.181
Birth weight strata			0.317
500 to 749 g	20 (23.3)	27 (20.0)	
750 to 999 g	30 (34.9)	61 (45.2)	
1,000 to 1,250 g	36 (41.9)	47 (34.8)	
Birth weight z-score	-0.399 (-0.755 to 0.292)	-0.266 (-0.824 to 0.292)	0.632
Small for gestational age	22 (25.6)	35 (25.9)	0.954
Sex, male	34 (39.5)	71 (52.6)	0.058
Maternal age, yr	28 (24 to 31)	27 (22 to 32)	0.270
Maternal race			0.483
Asian	1 (1.2)	0 (0)	
Black or African American	13 (15.1)	27 (20.0)	
White	71 (82.6)	107 (79.3)	
Other	0 (0)	1 (0.7)	
Unknown	1 (1.2)	0 (0)	
Maternal ethnicity, Hispanic or Latino	23 (26.7)	30 (22.2)	0.443
Maternal complications			
Multiple gestation	21 (24.4)	38 (28.1)	0.541
Gestational diabetes	1 (1.2)	12 (8.9)	0.022
Preexisting hypertension	10 (11.6)	18 (13.3)	0.873
Prolonged rupture of membranes	15 (17.4)	24 (17.8)	0.956
Chorioamnionitis	15 (17.4)	27 (20.0)	0.651
Preeclampsia	24 (27.9)	39 (28.9)	0.935
Antepartum hemorrhage	9 (10.5)	25 (18.5)	0.155
Maternal smoking	6 (7.0)	21 (15.6)	0.058
Maternal substance abuse	7 (8.1)	6 (4.4)	0.255
Antenatal corticosteroids	64 (74.4)	107 (79.3)	0.275
Cesarean section	59 (68.6)	104 (77.0)	0.165

Definition of abbreviation: IQR = interquartile range.

or equal to 0.05. All data analyses were performed using SAS version 9.4 software (SAS Institute Inc.).

Results

During the study period, 274 preterm infants underwent echocardiogram assessment at 7 days of age and survived to hospital discharge. Of these, 232 (85%) completed follow-up surveys, and 221 (81%) had sufficient follow-up data to determine the primary outcome of LRD. Characteristics of the 221 infants are presented in Table 1. The number of caregivers completing surveys at 6, 12, 18, and 24 months were 194, 172, 184, and 169, respectively. One hundred twenty-five caregivers completed all four surveys, 49 completed three surveys, 25 completed two surveys, and 22 completed only one survey. A comparison of subject characteristics of those completing only one survey versus those with more than one survey completed

is presented in Table E2. One hundred thirty-five infants met predefined criteria of LRD during the first 2 years of life (61%). Of these 135 infants, 50% ($n = 68$) had hospitalization for respiratory illness; 71% ($n = 96$) were diagnosed with asthma, reactive airways disease, or a BPD exacerbation by a physician; 60% ($n = 81$) were diagnosed with bronchiolitis, bronchitis, or pneumonia by a physician; and 69% ($n = 93$) met more than one criterion.

Although the overall numbers were small ($n = 13$), gestational diabetes was significantly overrepresented in the infants with LRD (9% vs. 1%; $P = 0.02$) (Table 1). There was a greater proportion of maternal smokers in the LRD group, but the difference did not reach statistical significance (16% vs. 7%; $P = 0.06$). None of the other prenatal factors were significantly different between the groups.

Postnatal outcomes during the neonatal hospitalization are provided in

Table 2. A higher proportion of LRD infants received surfactant (90% vs. 80%; $P = 0.05$). Evidence of PVD was present at 7 days of age in 41% ($n = 90$) of the infants. A greater proportion of infants with LRD had early PVD (50% vs. 27%; $P < 0.01$) and evidence of PH at 36 weeks PMA (17% vs. 6%; $P = 0.01$). There was greater proportion of LRD infants receiving invasive mechanical ventilation (MV) support at 7 days of age, but the difference was not statistically significant (44% vs. 31%; $P = 0.05$). Infants with LRD were more likely to have threshold retinopathy, longer duration of MV and oxygen support, and longer neonatal ICU (NICU) stays ($P < 0.01$). Forty-six percent ($n = 102$) of the cohort were diagnosed with classic BPD defined by the need for oxygen at 36 weeks PMA. A greater proportion of infants with LRD were diagnosed with classic BPD (52% vs. 37%; $P = 0.03$), and there were twice the proportion of infants with LRD who were diagnosed with severe BPD according to the

Table 2. Postnatal Hospitalization Data

	No Late Respiratory Disease ($n = 86$) [n (%) or Median (IQR)]	Late Respiratory Disease ($n = 135$) [n (%) or Median (IQR)]	P Value
Surfactant in delivery room	69 (80.2)	121 (89.6)	0.050
Mechanical ventilation support at 7 d	27 (31.4)	60 (44.4)	0.053
Echocardiogram findings at 7 d			
PFO	74 (86.0)	105 (77.8)	0.127
VSD	3 (3.5)	4 (3.0)	0.828
Measurable TRJV	7 (8.1)	15 (11.1)	0.472
RV hypertrophy	0 (0)	4 (3.0)	0.107
RV dilation	0 (0)	6 (4.4)	0.047
Septal wall flattening	20 (23.3)	55 (40.7)	0.007
PDA	26 (30.2)	50 (37.0)	0.299
PVD	23 (26.7)	67 (49.6)	0.001
PDA, medical treatment	36 (41.9)	50 (37.0)	0.052
PDA, surgical ligation	12 (14.0)	23 (17.0)	0.440
IVH (grade 3 or 4)	4 (4.7)	5 (3.7)	0.728
Necrotizing enterocolitis	10 (11.6)	25 (18.5)	0.171
Threshold retinopathy	5 (5.8)	24 (17.8)	0.010
BPD (NIH multilevel)			0.042
None	20 (23.3)	20 (14.8)	
Mild	34 (39.5)	45 (33.3)	
Moderate	20 (23.3)	30 (22.2)	
Severe	12 (14.0)	40 (29.6)	
BPD (dichotomous)			0.033
No BPD	54 (62.8)	65 (48.1)	
BPD	32 (37.2)	70 (51.9)	
PH at 36 wk PMA	5 (5.8)	23 (17.0)	0.014
Days on MV	6 (2–19)	20 (4–50)	<0.001
Total oxygen days (NICU)	60 (40–96)	87 (47–112)	0.013
Length of NICU stay, d	83 (69–100)	97 (79–124)	<0.001
Discharged on oxygen	45 (52.3)	76 (56.3)	0.563
Age successfully taken off oxygen, d	74 (46–138)	133 (59–265)	0.003

Definition of abbreviations: BPD = bronchopulmonary dysplasia; IQR = interquartile range; IVH = intraventricular hemorrhage; MV = mechanical ventilation; NICU = neonatal ICU; PDA = patent ductus arteriosus; PFO = patent foramen ovale; PH = pulmonary hypertension; PMA = postmenstrual age; PVD = pulmonary vascular disease; RV = right ventricle; TRJV = tricuspid regurgitant jet velocity; VSD = ventricular septal defect.

NIH multilevel definition (30% vs. 14%; $P < 0.01$).

The rate of LRD was higher among subjects with clinical evidence of PVD at both 7 days and 36 weeks. In the 81 patients with PVD at 7 days, 61 (75%) exhibited LRD. The proportion increases when one considers both MV and PVD at 7 days (31 of 38; 87%) with LRD. In the cohort, there were 32 infants (14%) who did not have early PVD, late PH, or BPD, but did have LRD. Further comparisons related to the NICU course between subjects with and without LRD are provided in Tables E3 and E4.

The parameter estimates from the multivariable logistic regression model selected to inform LRD using prenatal and early postnatal data including echocardiogram results from 7 days of age are presented in Figure 1 and Table E5. The final model selected included: maternal smoking, BPD status, antenatal corticosteroids, gestational diabetes, antepartum hemorrhage, multiple

gestation, study center, PVD at 7 days of age, PH at 36 weeks PMA, ventilator support at Day 7 of age, patent foramen ovale at Day 7 of age, and PVD plus MV at Day 7 of age. Gestational diabetes had the largest estimated association with LRD (odds ratio [OR], 10.7; confidence interval [CI], 1.3–90.3; $P = 0.03$), although only 13 mothers had this condition. PVD (OR, 3.1; CI, 1.5–6.2; $P < 0.01$) and MV support (OR, 2.6; CI, 1.3–5.4; $P < 0.01$) at 7 days were significantly associated with LRD. PH at 36 weeks was not significantly associated with the likelihood of LRD. The combined effect of PVD and MV at 7 days increased the odds of LRD to 8.1 (CI, 3.1–21.9; $P < 0.01$) compared with individuals with no PVD or MV at 7 days. Of the 13 infants born to mothers with gestational diabetes, five infants had PVD at 7 days, three infants were on MV at 7 days, and none had both. There was also a significant study site effect with infants hospitalized at Indiana hospitals exhibiting a 2.2 (CI, 1.1–4.3; $P = 0.02$)

increase in the odds of LRD. Severe BPD, compared with infants without BPD, had a 3.3 (CI, 1.4–8.2) increased odds of LRD. A comparison of the receiver operating characteristic curves for models using only prenatal and early postnatal covariates, BPD status (multilevel classification) alone, and early covariates plus BPD status (multilevel classification) for likelihood of LRD are presented in Figure 2. The early covariates model produced an AUC of 0.764. Adding BPD status to the model produced a modest increase to an AUC of 0.771, whereas BPD status alone discriminated likelihood of LRD with an AUC of 0.604 that was significantly smaller compared with the other two models ($P < 0.01$ for both).

Discussion

We found that 61% of preterm infants born before 34 weeks PMA and birthweights between 500 and 1,250 g exhibited LRD in the first 2 years after birth, and that both early echocardiogram evidence of PVD and MV at 7 days of age are each strongly associated with LRD during childhood. Additionally, infants receiving MV at 7 days of age who also had evidence of PVD had an eightfold increased odds of LRD over infants with neither MV nor PVD. Overall, prenatal and early postnatal (within 7 d after birth) covariates informed LRD with an AUC of 0.76. Although BPD status (by multilevel classification) determined at 36 weeks PMA was also associated with the risk of LRD in childhood, its prognostic power was not as great as the prenatal and early postnatal factors and did not significantly increase the ability to inform LRD when added to that model. These results demonstrate that early PVD and MV support at 7 days of age are strong risk factors for LRD, and these factors could provide practical prognostic information for caregivers and parents as well as identify high-risk infants for future clinical trials evaluating interventions to prevent or mitigate LRD.

These findings are important because they show that early perinatal factors, including evidence of PVD, not only are strong risk factors for BPD and PH at 36 weeks PMA (13, 14), but are also strongly associated with LRD, a highly clinically relevant morbidity measure (26). These results provide additional clinical evidence that PVD plays a critical role in the

Figure 1. Adjusted odds ratios (ORs) from three distinct logistic regressions modeling late respiratory diagnosis, based on 1) perinatal factors, 2) dichotomized bronchopulmonary dysplasia (BPD) diagnosis, and 3) the standard NIH-defined four-category BPD classification. Perinatal factors display the final multivariable model selected for prenatal factors and postnatal factors available within 7 days after birth. NIH BPD Categories shows the ORs for the univariable model with four levels of BPD (none, mild, moderate, severe), BPD Dichotomized shows the ORs for the univariable model with classic BPD diagnosis (no BPD categorizes as NIH none or mild vs. BPD categorized as NIH moderate or severe). Gestational diabetes and the combination of pulmonary vascular disease and mechanical ventilation support were the strongest prognosticators of late respiratory disease (OR, 10.7; confidence interval [CI], 1.3–90.3; and OR, 8.1; CI, 3.1–21.9, respectively; $P < 0.001$). Severe BPD significantly increased odds of late respiratory disease compared with those without BPD (OR, 3.3; CI, 1.4–8.2; $P = 0.008$). MV = mechanical ventilation; PFO = patent foramen ovale; PH = pulmonary hypertension; PMA = postmenstrual age; PVD = pulmonary vascular disease.

Figure 2. Receiver operating curves suggest that perinatal factors alone can inform late respiratory disease and bronchopulmonary dysplasia (BPD) status, but much earlier in the postnatal course. Logistic models: model including selected covariates from prenatal and early postnatal data, model using selected covariates plus BPD status (multilevel classification) at 36 weeks, and model using BPD status (multilevel classification) alone. ROC = receiver operating characteristic.

pathobiology of chronic lung disease after preterm birth and contributes to clinically relevant long-term respiratory outcomes in childhood (14, 17, 27–29). We further note that MV at 7 days was also strongly associated with subsequent LRD. The need for MV was previously found to be a strong predictor of BPD risk in a larger multicenter cohort (30), but this is among the first reports to demonstrate the association of MV support at Day 7 with long-term respiratory morbidity. It is unclear whether MV at 7 days is a marker of more severe disease or whether ventilator-induced lung injury contributes to disease risk.

Early perinatal factors were more closely associated with LRD than BPD status alone, thus allowing for earlier and more precise identification of high-risk preterm infants. There has been recent controversy regarding how useful the current NIH definition of BPD applied at 36 weeks PMA prognosticates clinically relevant outcomes, including LRD during childhood (6, 9, 10, 31, 32). There is a need to improve the definition of BPD to better prognosticate late respiratory outcomes and to provide a

more reliable endpoint for clinical trials. In addition, identification of high-risk infants earlier in their course may provide a therapeutic window for applying established or novel therapies to improve late respiratory morbidities (33). Such approaches would also allow for the use of more selective care strategies (“precision medicine”), better design of clinical trials, and the development of more effective interventions.

Previous studies have shown that PH is commonly associated with established BPD (13, 14, 17, 34); however, the early recognition of disrupted pulmonary vascular growth in preterm infants and its contribution to the pathogenesis of LRD has also been demonstrated (11, 14, 35, 36). PVD in preterm infants is characterized by altered lung vascular development, growth, structure, or function, which may precede the onset of measurable PH (12, 37). Exposure to adverse stimuli during the prenatal and/or early postnatal periods has been shown to impair normal pulmonary vascular development (35–38). This disruption of normal pulmonary vascular development in association with preterm birth is an important determinant of the pathobiology of BPD and late respiratory outcomes. Recent data have shown that among infants evaluated with echocardiogram at 12 months of age, those born preterm had lower pulmonary artery acceleration time than infants born at term, and infants with BPD had lower measures compared with non-BPD preterm infants, providing evidence that PVD persists to 1 year of age in some preterm infants (39). Children 11–14 years of age who were born preterm and developed BPD had greater peak tricuspid regurgitation velocity than those born preterm without BPD and those born at term (40), suggesting that echocardiogram evidence of PVD, below thresholds generally applied for traditional diagnosis of PH, persist into childhood.

The cohort reported in this study represents a 2-center subset of a larger five academic center cohort who received echocardiogram screening at 7 days of age and 36 weeks PMA by study protocol. We have previously reported for the larger cohort ($n = 587$), that maternal age, race, smoking, and diabetes status, as well as GA and multiple gestation pregnancies increased risk for LRD (AUC, 0.66) (6). The current study reveals that adding early postnatal factors including evidence of

PVD and MV support at 7 days to the model substantially improves its accuracy (AUC, 0.764), and suggests these factors may contribute to late disease.

Recently, the NIH Prematurity and Respiratory Outcomes Program (PROP) conducted a multicenter prospective study ($n = 724$) to identify early predictors of respiratory morbidity in the first year after birth (7). As we observed, these investigators found that perinatal factors (those available in the first day after birth, including male sex, intrauterine growth restriction, maternal smoking, race/ethnicity, intubation at birth, and public insurance) were good predictors of late respiratory morbidity (AUC, 0.858). Thus, our study validates the premise that infants with high risk for late respiratory morbidity can be identified soon after preterm birth. Contrary to our study, the PROP study found that BPD status alone was as good or better than perinatal factors (AUC, 0.907). Reasons for this discrepancy may be related to differences in cohort selection. The PROP cohort enrolled infants with between 23 and 29 weeks GA, whereas we enrolled infants less than 34 weeks GA, but between 500 and 1,250 g. These inclusion criteria or other factors, such as related to referral patterns to the NICUs in this study, likely contributed to an overrepresentation of small for GA infants in this study cohort. Additionally, there were subtle differences in the measures defining late respiratory morbidity, and our study examined respiratory morbidities during the first 2 years after birth, whereas the PROP cohort only examined outcomes during the first year. Based on these differences, one could speculate that either BPD status is a less accurate predictor of outcome for slightly more mature preterm infants (29–34 wk GA) or that BPD is a better predictor of earlier respiratory morbidity (in the first year of life) rather than for later childhood respiratory morbidity (at 2 yr).

Potential limitations of this study include possible recall bias and the reliability of data collected by surveys, including maternal smoking status and the data used to define LRD. Additionally, not all questions were completely answered in all surveys, which limited the number of participants included in the model generation. Furthermore, we included subjects with at least one survey completed,

which limited the ascertainment of LRD in some subjects (subjects with one survey had lower rate of LRD compared with those with more than one survey). We did not collect data on socioeconomic status of participants and their families. There are likely complex and compounding associations between socioeconomic status, smoking, diabetes, and other environmental exposures on late respiratory outcomes and on access to professional medical care in follow-up, which could impact the responses to questions defining LRD. Center of care was found to be a risk factor for the outcome of interest because it was in our previous report (14), and likely relates to differences in demographics, clinical practice, and/or an altitude effect. The diagnosis of PVD and PH used in this study relied on traditional echocardiographic measures that detect

evidence of pressure overload (septal wall flattening and estimated pulmonary artery pressure derived from the tricuspid regurgitant jet), which have been shown to be reliable echocardiographic markers of PVD in preterm infants (41). Emerging noninvasive measures that assess other aspects of RV afterload may help to further refine the specific diagnosis of PVD or PH. Whether PVD is a causative factor in the development of LRD or merely an association related to other factors cannot be determined from these data.

In conclusion, the combination of early echocardiographic evidence of PVD with antenatal determinants and the need for MV at Day 7 are strong risk factors for LRD. These findings suggest that the echocardiogram at 1 week of age, especially in those who remain on invasive MV, may

be a useful tool to identify preterm infants at high risk for late respiratory outcomes. Although BPD status at 36 weeks PMA is also associated with LRD, we speculate that the risk of LRD can be determined early in the postnatal course of preterm infants, allowing for more timely identification of high-risk infants and selected implementation of clinical strategies to prevent or mitigate poor respiratory outcomes. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Marci Sontag, Joshua Miller, Lindsey Morrow, Lucy Fashaw, Leslie Dawn Wilson, and James Thorpe for their excellent support of this study. The authors are indebted to all the infants and their families for their participation in this study.

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