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Pulmonary Artery Hypertension in Formerly Premature Infants With Bronchopulmonary Dysplasia: Clinical Features and Outcomes in the Surfactant Era

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ABSTRACT

BACKGROUND. Although abnormal pulmonary vascular structure and function in preterm infants with bronchopulmonary dysplasia may predispose infants to pulmonary artery hypertension, little is known about the characteristics and outcomes of bronchopulmonary dysplasia-associated pulmonary artery hypertension in the surfactant era.

METHODS. We studied 42 premature infants (<32 weeks of gestation) with bronchopulmonary dysplasia who were diagnosed as having pulmonary artery hypertension ≥2 months after birth, between 1998 and 2006, at a median age of 4.8 months. Pulmonary artery hypertension was graded through echocardiography for all patients; 13 patients also underwent cardiac catheterization.

RESULTS. Eighteen (43%) of 42 patients had severe pulmonary artery hypertension (systemic or suprasystemic right ventricular pressure). Among 13 patients who underwent catheterization, the mean pulmonary artery pressure was 43 ± 8 mm Hg and the pulmonary vascular resistance index was 9.9 ± 2.8 Wood units. In 12 patients, pulmonary artery pressure and pulmonary vascular resistance improved with 100% oxygen and 80 ppm inhaled nitric oxide but remained elevated. The pulmonary vascular resistance index decreased to 7.9 ± 3.8 Wood units in 100% oxygen and to 6.4 ± 3.1 Wood units with the addition of nitric oxide. Sixteen patients (38%) died during the follow-up period. Estimated survival rates were 64% ± 8% at 6 months and 53% ± 11% at 2 years after diagnosis of pulmonary artery hypertension. In multivariate analyses, severe pulmonary artery hypertension and small birth weight for gestational age were associated with worse survival rates. Among 26 survivors (median follow-up period: 9.8 months), pulmonary artery hypertension was improved, relative to its most severe level, in 24 patients (89%).

CONCLUSION. Premature infants with bronchopulmonary dysplasia and severe pulmonary artery hypertension are at high risk of death, particularly during the first 6 months after diagnosis of pulmonary artery hypertension.

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Key Words
pulmonary vascular disease, atrial septal defect, chronic lung disease, prematurity

Abbreviations
BPD—bronchopulmonary dysplasia
NO—nitric oxide
PA—pulmonary artery
PAH—pulmonary artery hypertension
PVR—pulmonary vascular resistance
RV—right ventricle
SGA—small for gestational age
WU—Wood unit

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The advent of exogenous surfactant therapy and advances in critical care management have led to increased survival rates for premature infants but also have changed the pathologic features and clinical course of chronic lung disease of prematurity, known as bronchopulmonary dysplasia (BPD). Historically, oxygen toxicity and ventilator-induced injury characterized chronic lung disease in premature infants.[1,2] In the surfactant era, infants who are much less mature are surviving, and the normal sequence of lung development is disrupted.[3] There are substantial histologic differences in this "new" BPD, compared with the "old" BPD, including reductions in the size and number of alveoli.[1,2,4–6] Respiratory morbidity is common in patients with BPD, who often present with recurrent respiratory infections, airway hyperresponsiveness, and exercise intolerance.[7–10]

The pulmonary vasculature is also abnormal in infants with BPD. In conjunction with the abnormally small size and number of gas exchange units in the lungs of infants with BPD, there are deficiencies in the number and size of intraacinar pulmonary arteries (PAs), which are responsible for a significantly reduced total cross-sectional area of the pulmonary vascular bed.[3,11,12] Although a wide range of vascular abnormalities may be found in these patients, it is generally thought that the reduction of the vascular cross-sectional area and alveolar hypoxia result in structural remodeling of the pulmonary vasculature.[3,6] Evidence also suggests increased pulmonary vascular tone and heightened vasoreactivity well beyond infancy in patients with BPD.[6]

Changes in neonatal intensive care practices have contributed additional factors that predispose premature infants to increased pulmonary vasoconstriction. With recognition of the role of supplemental oxygen in retinopathy of prematurity, target oxygen saturations for premature infants have decreased.[13,14] Premature infants with BPD, and even those without, are known to experience significant severe hypoxemia.[15–17] Most of these episodes occur with sleep and feeding and remain undetected with the usual methods modern NICUs use to determine the need for supplemental oxygen therapy at home.[18] These episodes of intermittent severe hypoxia likely lead to increased pulmonary vascular tone, compounding the structural vascular abnormalities described above.

Although the mechanisms responsible for elevated pulmonary vascular resistance (PVR) and altered reactivity remain incompletely understood, the development of PA hypertension (PAH) is a recognized and sometimes serious complication of BPD that can contribute significantly to the morbidity and mortality rates for preterm infants.[19,20] Despite the potential importance of PAH in this patient population, relatively little is known about the prevalence of and risk factors for PAH in formerly premature infants with BPD. Several small reports concerning the clinical features and outcomes of patients with PAH and BPD were published in the 1980s,[19,21–24] before the routine use of surfactant, alternative modes of mechanical ventilatory support, and adjunctive agents such as inhaled nitric oxide (NO) and widespread concerns about oxygen toxicity.[3] Therefore, these series may not reflect the population of patients surviving after extremely premature birth today. The purpose of this report is to describe the spectrum and outcomes of PAH in formerly preterm infants with BPD in the current era.

METHODS

Patients

We ascertained patients who were born at an estimated gestational age of ≤32 weeks, had BPD, and were diagnosed as having PAH between 1998 and 2006 at Children's Hospital Boston or affiliated delivery hospitals covered by the cardiology consultation service of Children's Hospital, Brigham and Women's Hospital, and Beth Israel Deaconess Medical Center. BPD was defined as neonatal respiratory distress treated with mechanical ventilation during the newborn period, with the characteristic radiographic findings of pulmonary hyperexpansion with scattered areas of atelectasis and focal emphysema and with a requirement for supplemental oxygen therapy beyond 30 days of age.[2] BPD severity was graded according to the summary recommendations of the National Heart, Lung, and Blood Institute workshop as mild, moderate, or severe.[2]

PAH was diagnosed on the basis of elevated PA pressure measured directly at the time of cardiac catheterization or echocardiograms demonstrating elevated right ventricle (RV) pressure. We included only patients with one or both of these findings beyond the postnatal age of 2 months. Electrocardiographic evidence of RV hypertrophy alone was not sufficient for the diagnosis of PAH. Patients with known structural airway or lung anomalies, congenital anomalies of the PAs or pulmonary veins, major systemic vessel-to-PA collateral vessels, congenital heart disease (except those with a patent foramen ovale or atrial septal defect), severe liver disease, or persistent pulmonary hypertension of the newborn were excluded. Patients were also excluded if RV hypertension was diagnosed with echocardiography but a contemporaneous catheterization revealed normal RV pressure or if the diagnosis of elevated RV pressure was made before the age of 2 months but there was no subsequent echocardiogram or catheterization confirming persistently elevated RV pressure at >2 months of age.

Echocardiography

Standard cross-sectional and Doppler echocardiography was performed for all patients. A full anatomic survey was performed to evaluate cardiac and pulmonary vascular anatomic features. RV pressure was estimated through continuous wave interrogation of the tricuspid

regurgitant jet, if present, and calculation of a systolic RV-to-right atrium pressure gradient by using the modified Bernoulli equation (pressure gradient = 4 × jet velocity^2). If no tricuspid regurgitation was present or if the regurgitant jet could not be interrogated adequately, then RV pressure was estimated on the basis of ventricular septal position and was related to systolic systemic arterial pressure measured noninvasively or through direct arterial pressure monitoring if an arterial line was in place. RV pressure assessed on the basis of septal position was graded as <50% of the systemic pressure if the interventricular septum was round at end-systole, ≥50% but <100% of the systemic pressure if there was end-systolic flattening of the interventricular septum, and ≥100% of the systemic pressure if the interventricular septum bowed into the left ventricle at end-systole.[25] All echocardiograms were reviewed offline by a single echocardiographer.

Cardiac Catheterization and Vasoreactivity Testing

For a subset of patients with specific clinical indications, such as those with severe respiratory disease and severe PAH on echocardiograms or with known or suspected cardiovascular anomalies requiring further evaluation, cardiac catheterization was performed with conscious sedation or general anesthesia. Right heart and systemic arterial pressures and saturations were measured directly. Pulmonary and systemic blood flows were estimated either with the Fick equation, by using assumed oxygen consumption, or through thermodilution and were indexed to body surface area. PVR indexed to body surface area was calculated as PVR index (in Wood units [WUs]) = (mean PA pressure − mean left atrial or PA wedge pressure [in millimeters of mercury])/indexed pulmonary blood flow (in liters per minute per meter^2). Pulmonary vascular reactivity was tested first by administering 100% oxygen and then by adding inhaled NO (typically 80 ppm), repeating measurements, and recalculating cardiac index, pulmonary blood flow, and PVR. Each condition was maintained for ≥10 minutes before data acquisition.

Pulmonary Artery Hypertension

To allow for common categorization of PAH severity in patients who underwent echocardiography alone and those who underwent catheterization as well, PAH was graded for all patients according to the scale of RV pressure estimated on the basis of septal position, that is, normal, elevated but <50% of systemic pressure, ≥50% but <100% of systemic pressure, or ≥100% of systemic pressure. A patient was reported to have an improvement in the severity of PAH only if the estimated or directly measured RV pressure decreased to a lower grade. Similarly, a patient was reported to have progression of PAH only if the grade increased during the study period.

Data Analyses

Outcomes assessed included survival, progression or improvement in severity of PAH, and reactivity to inhaled pulmonary vasodilators. Independent variables assessed included gestational age at birth, birth weight, small birth weight for gestational age (<3rd percentile), duration of mechanical ventilation, use of high-frequency ventilation, tracheostomy, patent ductus arteriosus treated with indomethacin or surgery, necrotizing enterocolitis, gastrostomy tube placement, grade III or IV intraventricular hemorrhage, method of delivery, maternal hypertension, maternal age, multiple-gestation pregnancy, and oligohydramnios. Independent variables were also analyzed for association with severe PAH. In survival analyses, severity of PAH was treated as an independent variable. For comparison of continuous and categorical variables between groups, the independent-samples *t* test and Fisher's exact test, respectively, were used. For comparison of hemodynamic data before and after vasoreactivity testing during cardiac catheterization, paired *t* test analysis was performed, with adjustment for multiple comparisons. Time-dependent outcomes were assessed with Kaplan-Meier analysis, with comparisons between factors using the log-rank test, and with multivariate Cox regression analysis. Data are presented as mean ± SD, median and range, or frequency. Odds ratios are presented with 95% confidence intervals.

The study was approved by the Children's Hospital Committee on Clinical Investigation. We had full access to the data and take full responsibility for its integrity.

RESULTS

Patients

A total of 42 premature infants (21 male and 21 female) with BPD were diagnosed as having PAH between 1998 and 2006 and met the inclusion criteria for this study. The median gestational age at birth was 26 weeks (range: 23–32 weeks), and the median birth weight was 701 g (range: 355–1320 g). Eleven patients (26%) were small for gestational age (SGA) at birth, defined as weight of <3rd percentile for the estimated gestational age. The majority of patients were born at other hospitals and transported to Children's Hospital for additional treatment (Table 1). Demographic and diagnostic characteristics of the study population are summarized in Table 1.

Pulmonary Artery Hypertension

PAH was diagnosed at a median postnatal age of 4.8 months (range: 2.6–79 months), with all except 4 patients (2 with severe PAH and 2 with mild PAH) being <1 year of age. All patients were evaluated with echocardiography, and 13 also underwent cardiac catheterization. For 6 of the 42 patients (all with mild PAH), electrocardiograms obtained near the time of echocardiographic diagnosis did not show evidence of RV hy-

TABLE 1 **Demographic and Diagnostic Characteristics of 42 Premature Infants With BPD and PAH**

Variable	All Patients ($n = 42$)	Severe PAH ($n = 18$)[a]	Less-Than-Severe PAH ($n = 24$)
Gestational age at birth, median (range), wk	26 (23–31)	25.5 (23–31)	26.5 (23–32)
Birth weight, median (range), g	702 (355–1320)	702 (525–955)	696 (355–1320)
Weight of <3rd percentile for age, *n* (%)	11 (26)	8 (44)	3 (13)
Male, *n* (%)	21 (50)	11 (61)	10 (42)
BPD severity, *n* (%)[b]			
Severe	16 (41)	8 (47)	8 (36)
Moderate	22 (56)	8 (47)	14 (64)
Mild	1 (3)	1 (6)	0 (0)
Mechanical ventilation for >2 mo, *n* (%)	12 (29)	7 (39)	5 (21)
Ever supported with high-frequency ventilation, *n* (%)	22 (52)	13 (72)	9 (38)
Tracheostomy, *n* (%)	6 (14)	5 (25)	1 (4)
Patent ductus arteriosus treated with indomethacin or surgery, *n* (%)	26 (63)	10 (56)	16 (67)
Grade III or IV intraventricular hemorrhage, *n* (%)	5 (12)	1 (6)	4 (17)
Necrotizing enterocolitis, *n* (%)	10 (24)	2 (11)	8 (33)
Twin-gestation pregnancy, *n* (%)	6 (14)	1 (6)	5 (21)
Atrial septal defect, *n* (%)	3 (7)	2 (11)	1 (4)
Trisomy 21, *n* (%)	2 (5)	2 (11)	0 (0)
Born at affiliated delivery hospital covered by Children's Hospital cardiology service, *n* (%)	16 (38)	4 (22)	12 (50)
Diagnosed with PAH after discharge from initial postnatal hospitalization, *n* (%)	26 (62)	11 (61)	15 (63)

[a] Systemic or suprasystemic RV pressure was documented at some point during the study period.

[b] BPD severity, graded according to the recommendations of the National Heart, Lung, and Blood Institute workshop,[2] could not be differentiated between moderate and severe for 3 patients (1 with severe PAH and 2 with less-than-severe PAH) who required supplemental oxygen at gestational age of 36 weeks but for whom the fraction of inspired oxygen at that time could not be determined from available records.

pertrophy. At the time of diagnosis, RV systolic pressure was systemic or suprasystemic for 15 patients (36%), ≥50% but <100% of systemic pressure for 23 (55%), and elevated but <50% of systemic pressure for 4 (9%). For 8 patients, the severity of PAH progressed at some point during the study period; for 28 patients, a decrease in the grade of PAH was observed and was sustained at the most recent follow-up evaluation. Of the 42 patients, 18 (43%) were observed to have systemic or suprasystemic RV pressure at some point during the study period. Patients who were SGA at birth were significantly more likely to have systemic or suprasystemic RV pressure than were patients with birth weights above the 3rd percentile for age (8 of 11 patients [73%] vs 10 of 31 patients [32%]; odds ratio: 5.6; 95% confidence interval: 1.2–25.7; $P = .03$).

Pulmonary Vascular Reactivity

Hemodynamic data obtained during catheterization are summarized in Table 2. For all 13 patients who underwent catheterization, pulmonary vascular reactivity testing was performed with 100% oxygen ($n = 12$) and/or 80 ppm inhaled NO ($n = 13$). At baseline, the average mean PA pressure was 43 ± 8 mm Hg, the average PVR index was 9.9 ± 2.8 WUs, and the average PVR/systemic vascular resistance ratio was 0.51 ± 0.18. For 12 of 13 patients, PA pressure and PVR decreased with vasodilator testing but remained elevated (Table 2). When indexed PVR decreased, the majority of the change (to 7.9 ± 3.8 WUs; 29% ± 28% decrease from baseline) was observed with administration of 100% oxygen, with an additional small decrease (to 6.4 ± 3.1 WUs) after the addition of inhaled NO (Fig 1). In 1 case, PVR did not change with hyperoxia but decreased >30% after the addition of inhaled NO. Overall, there was a significant decrease in PVR in response to 100% oxygen, compared with baseline values. With the addition of 80 ppm of inhaled NO, the mean PA pressure, RV systolic pressure, and PVR/systemic vascular resistance ratio also decreased to levels significantly lower than at baseline.

With a single exception, the only patients for whom PVR normalized (<4 WUs) with vasodilator testing were 3 patients with secundum atrial septal defects, in whom PA pressure remained elevated but left-right shunting and pulmonary blood flow increased. For these 3 patients, the pulmonary/systemic blood flow ratio increased from 1.1 to 1.3 at baseline to 1.7 to 2.1 with 100% oxygen and 80 ppm inhaled NO.

Among patients diagnosed as having PAH through echocardiography alone, 4 had ≥1 study during which serial evaluation was performed before and after addition of inhaled NO, in the cardiac ICU. Two of those patients had lower RV pressure while receiving inhaled NO than before the addition of NO.

Survival Rates

Cross-sectional follow-up data were obtained a median of 5.2 months (range: 0.1–98 months) after the diagnosis

TABLE 2 **Cardiac Catheterization and Pulmonary Vascular Reactivity Data for 13 Patients With BPD and PAH**

Patient	Condition	Cardiac Index, L/min per m²	Aortic Pressure, mm Hg	RV Pressure, mm Hg	Mean PA Pressure, mm Hg	PCW Pressure, mm Hg	PVR Index, WUs	PVR/SVR Ratio
1	RA	3.0	112	90	69	6	21	0.74
	100% O_2	2.6	125	60	36	6	11.5	0.30
	NO	2.6	125	53	32	5	10.4	0.27
	Change from RA to 100% O_2, %	−12	+12	−33	−48	0	−45	−59
	Change from RA to NO, %	−13	+12	−41	−54	−17	−50	−64
2	100% O_2	4.0	80	110	58	12	11.5	0.96
	NO	2.6	75	56	42	9	12.7	0.60
	Change from 100% O_2 to NO, %	−35	−6	−49	−28	−25	10	−37
3[a]	RA	3.2	80	82	59	15	12.9	0.83
	100% O_2	3.5	83	60	40	11	3.9	0.24
	NO	4.5	85	65	35	16	2.0	0.16
	Change from RA to 100% O_2, %	9	4	−27	−32	−27	−70	−71
	Change from RA to NO, %	41	6	−21	−41	7	−84	−81
4	RA	3.3	90	100	46	5	12.4	0.72
	100% O_2	4.1	120	125	64	3	14.9	0.80
	NO	3.6	76	67	34	3	8.6	0.52
	Change from RA to 100% O_2, %	24	33	25	39	−40	20	12
	Change from RA to NO, %	9	−16	−33	−26	−40	−31	−28
5[a]	RA	2.1	85	50	30	11	7.1	0.24
	NO	2.5	89	54	31	12	4.1	0.17
	Change from RA to NO, %	19	5	8	3	9	−42	−31
6	RA	3.2	80	55	38	13	8.6	0.66
	100% O_2	5.8	97	73	50	15	6.6	0.45
	NO	4.7	110	70	50	14	7.6	0.48
	Change from RA to 100% O_2, %	81	21	33	32	15	−23	−32
	Change from RA to NO, %	47	38	27	32	8	−11	−27
7	RA	3.8	98	50	38	6	8.4	0.43
	100% O_2	4.1	90	54	38	7	7.6	0.49
	NO	3.8	105	49	34	6	7.4	0.41
	Change from RA to 100% O_2, %	8	−8	8	0	17	−10	14
	Change from RA to NO, %	0	7	−2	−11	0	−12	−4
8	RA	2.7	94	50	35	11	8.9	0.32
	100% O_2	2.6	100	50	35	13	8.5	0.32
	NO	2.5	92	45	32	11	8.4	0.30
	Change from RA to 100% O_2, %	−4	6	0	0	18	−4	−3
	Change from RA to NO, %	−7	−2	−10	−9	0	−5	−7
9	RA	2.4	85	60	42	11	13.0	0.47
	100% O_2	2.3	92	54	38	16	9.5	0.34
	NO	2.5	89	50	34	14	8.0	0.30
	Change from RA to 100% O_2, %	−4	8	−10	−10	45	−26	−28
	Change from RA to NO, %	4	5	−17	−19	27	−38	−35
10[a]	RA	4.4	76	67	45	11	6.1	0.57
	100% O_2	6.4	82	65	42	16	2.0	0.23
	NO	6.0	91	68	40	16	2.3	0.22
	Change from RA to 100% O_2, %	45	8	−3	−7	45	−67	−60
	Change from RA to NO, %	36	20	1	−11	45	−62	−61
11	RA	2.8	110	76	50	10	14.3	0.58
	100% O_2	2.8	117	55	37	11	9.3	0.29
	NO	2.7	110	46	29	12	6.3	0.22
	Change from RA to 100% O_2, %	0	6	−28	−26	10	−35	−50
	Change from RA to NO, %	−4	0	−39	−42	20	−56	−61
12	RA	3.4	100	60	35	11	7.1	0.35
	100% O_2	4.1	96	42	24	10	3.4	0.20
	NO	3.8	86	35	22	10	3.2	0.20
	Change from RA to 100% O_2, %	21	−4	−30	−31	−9	−52	−44
	Change from RA to NO, %	12	−14	−42	−37	−9	−55	−44
13	RA	3.2	90	70	49	15	10.6	0.40
	100% O_2	3.1	75	61	44	13	10.0	0.78
	NO	3.4	69	60	38	16	6.5	0.60
	Change from RA to 100% O_2, %	−3	−17	−13	−10	−13	−6	94
	Change from RA to NO, %	6	−23	−14	−22	−7	−39	49
All, mean ± SD	RA	3.2 ± 0.7	90 ± 10	66 ± 16	43 ± 8	10.8 ± 3.1	9.9 ± 2.8	0.51 ± 0.18
	100% O_2	3.9 ± 1.3	94 ± 14	68 ± 25	43 ± 11	11.5 ± 3.9	7.9 ± 3.8	0.45 ± 0.26
	NO	3.6 ± 1.1	90 ± 13	55 ± 11	35 ± 7	11.6 ± 4.1	6.4 ± 3.1	0.34 ± 0.16
	Change from RA to 100% O_2, %	15 ± 28	6 ± 13	−6 ± 21	−8 ± 26	5 ± 26	−29 ± 28[b]	−21 ± 48
	Change from RA to NO, %	11 ± 23	2 ± 16	−16 ± 23[b]	−18 ± 21[b]	4 ± 22	−35 ± 27[c]	−33 ± 33[b]

PCW indicates pulmonary capillary wedge; SVR, systemic vascular resistance; RA, room air.

[a] These 3 patients had atrial septal defects, with pulmonary/systemic blood flow ratios of 1.1 to 1.3 at baseline, which increased to 1.7 to 2.1 with oxygen and NO.

[b] $P \leq .01$, compared with baseline.

[c] $P \leq .001$, compared with baseline.

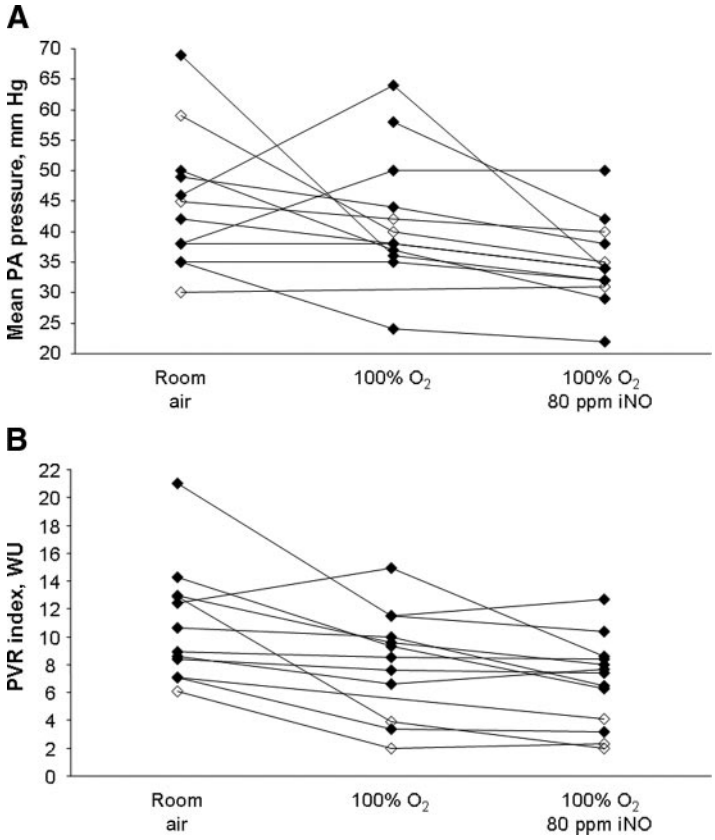

FIGURE 1
Line graphs demonstrating changes in mean PA pressure (A) and PVR index (B) in 13 patients with BPD and PAH who underwent cardiac catheterization and vasoreactivity testing with 100% oxygen and 80 ppm inhaled NO (iNO). The open symbols represent the 3 patients with secundum atrial septal defects who underwent catheterization.

of PAH, at a median age of 10.9 months (range: 5.1–101 months). Sixteen patients (38%) died during the follow-up period, 13 within 2 months after diagnosis. For 14 of those patients, PAH was determined to be a proximate contributing factor to death, often in concert with respiratory failure; the other 2 patients had relatively mild PAH (<50% of systemic pressure) and died as a result of respiratory failure ($n = 1$) or sepsis ($n = 1$).

By Kaplan-Meier analysis, survival rates after diagnosis were 85% ± 6% at 1 month, 70% ± 7% at 2 months, 64% ± 8% at 6 months, 61% ± 8% at 1 year, and 52% ± 11% at 2 and 3 years (Fig 2A). Independent variables that were associated significantly with or approached significance for association with shorter survival times in log-rank testing included severe PAH (systemic or suprasystemic RV pressure) at any time during the study period ($P = .003$), SGA status (birth weight of <3rd percentile for age) ($P = .03$), previous support with high-frequency ventilation at any time ($P = .05$), and systemic or suprasystemic RV pressure at the time of PAH diagnosis ($P = .065$). Of note, severe BPD was not associated with worse survival rates. In multivariate Cox regression analysis, severe PAH (systemic or suprasystemic RV pressure) at any time during the study period ($P = .003$) was the only independent predictor of shorter survival times, although SGA status approached significance ($P = .07$). The multivariate Cox regression models were also performed while controlling for gestational age, SGA, and severity of BPD, and the presence of systemic or suprasystemic RV pressure at any time during the study period remained a significant independent predictor of shorter survival times. As depicted in Fig 2B, survival rates determined through Kaplan-Meier analysis for patients with systemic or suprasystemic RV pressure were 65% ± 12% at 1 month, 44% ± 12% at 6 months, 37% ± 12% at 1 year, and 25% ± 13% at 2 and 3 years; for patients with less-than-severe PAH, survival rates were 100% at 1 month and 78% ± 9% at ≥6 months.

Follow-up Findings and Management

Among 26 surviving patients, the median duration of follow-up monitoring was 9.8 months (range: 1–98 months) after the diagnosis of PAH. RV pressure was normal in 5 of those patients (19%), <50% of systemic pressure in 16 (62%), ≥50% but <100% of systemic pressure in 3 (12%), and ≥100% of systemic pressure in 2 (8%). The severity of PAH was improved for 24 of those patients (89%), compared with the most-severe level of PAH. Seven patients with severe PAH at any time during the study period were alive at the most recent follow-up evaluation. Two of those patients continued to have RV pressure ≥100% of systemic pressure, 1 had RV pressure ≥50% but <100% of systemic pressure, and 4 had RV pressure <50% of systemic pressure, 2 of whom had atrial septal defects that had been closed.

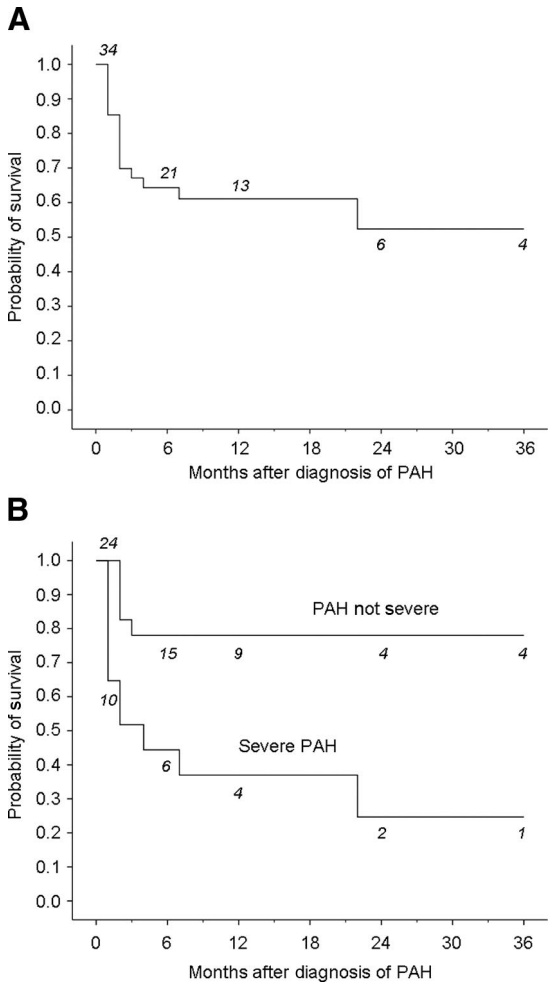

FIGURE 2
Kaplan-Meier graphs demonstrating the probability of survival from the time of diagnosis of PAH for patients with BPD and PAH, including all patients ($n = 42$) (A) and patients with severe PAH at any time ($n = 18$) and those with less-than-severe PAH ($n = 24$) (B). The numbers of patients at risk at 1, 6, 12, 24, and 36 months are indicated along the respective curves.

DISCUSSION

Spectrum and Outcomes of PAH in Infants and Children With BPD

The prevalence of PAH in formerly premature infants with BPD is not known.[4,26,27] In this study, we reviewed our experience from 1998 to 2006 with 42 infants with BPD for whom a diagnosis of PAH was confirmed through echocardiography and/or cardiac catheterization at >2 months of age. The spectrum of PAH in these patients was wide; almost one half had severe PAH, with systemic or suprasystemic RV pressure, whereas 4 had only mild PAH, with RV pressure <50% of systemic pressure, and the remainder had RV pressure between 50% and 100% of systemic pressure. The mortality rate was high, with only 64% ± 8% surviving 6 months after the diagnosis of PAH. As might be expected, the survival rate was significantly worse among patients with severe PAH, and there was a trend toward worse outcomes among infants who were SGA at birth. Among surviving patients, most demonstrated some degree of improvement in PAH during the follow-up period.

Little is known about risk factors for PAH among formerly premature infants with BPD, but there are several published reports concerning the clinical features and outcomes of such patients. Most of those were small series that included primarily infants born in the 1980s, before the routine use of surfactant and alternative modes of mechanical ventilation and widespread concerns about oxygen toxicity. Therefore, these reports may not reflect the characteristics and treatment of patients surviving after extremely premature birth in the current era. A study published by Fouron et al[22] in 1980, for example, showed a mortality rate of 50% in infants with BPD who had PAH at >4 months of life. In 2 separate reports of patients with BPD evaluated with cardiac catheterization, Berman et al[23] reported mean PA pressures as high as 89 mm Hg at 10 to 28 months of age and persistently elevated PA pressures at a mean age of 5.8 years.[4] Abman et al[21] reported an average mean PA pressure of 48 mm Hg in a series of 6 young children with BPD who underwent cardiac catheterization. These reports, published >2 decades ago, demonstrated that elevated PA pressure may be a long-term and significant problem in preterm infants with BPD. More recently, Subhedar and Shaw[28] demonstrated that premature infants with BPD had higher echocardiographically derived PA pressures than did premature infants without BPD.

Patients with BPD and PAH in the setting of an atrial septal defect are a clinically distinct subgroup. Of 3 such patients in this series, 2 had severe PAH but were highly reactive to 100% oxygen and inhaled NO and had RV pressure <50% of systemic pressure after closure of the atrial septal defect.

Anatomic and Functional Factors Contributing to PAH in Infants With BPD

Intrinsic and secondary abnormalities of the pulmonary circulation in premature infants with BPD may predispose the infants to PAH. BPD associated with prematurity in the surfactant era is characterized by inhibition of lung development, with altered structure, growth, and function of the distal airspaces and vasculature. Although intrinsic abnormalities of lung growth and function have been characterized, the vasculature of the immature lung is also susceptible to the injury that is seen in BPD.[3,12,29] For example, endothelial cells are especially vulnerable to injury via hyperoxia and inflammation, which may contribute to smooth muscle cell proliferation and incorporation of myofibroblasts into the vessel wall.[11,12] Structural abnormalities of the pulmonary vasculature lead to narrowing of vessel diameters and decreased vascular compliance. Decreased angiogenesis is another consequence of BPD and may

contribute to reduced vascular cross-sectional area.[3] Functionally, these factors contribute to elevated PVR.

The pulmonary circulation in patients with BPD is abnormally responsive to oxygen and other pulmonary vasodilators and may remain so long beyond infancy.[3,6,21,23] In 1985, Abman et al[21] demonstrated significant decreases in PA pressure in response to high concentrations of inspired oxygen, with similar benefits conferred by lower levels of supplemental oxygen. A study by Mourani et al,[6] however, indicated that a subset of this population receiving oxygen therapy would continue to have elevated baseline PA pressure, as well as the clinical symptoms associated with PAH. With the addition of inhaled NO to 100% oxygen, their patients experienced additional improvement in PA pressure and PVR, in many cases to normal or nearly normal levels.[6] In the present study, we found that 100% inspired oxygen significantly decreased PVR but not mean PA pressure and the addition of inhaled NO led to additional improvement. Other investigators demonstrated improvement in PVR in patients with BPD and PAH in response to prostacyclin[12,20] and variable responsiveness to calcium channel blockers.[6,30]

Evaluation of PAH in Infants With BPD

The prevalence of and risk factors for PAH in infants with BPD are not known, which complicates the development of an effective screening strategy. In the present study, almost one half of the 18 patients with systemic or suprasystemic RV pressure were SGA, which suggests that SGA infants may be at increased risk for severe PAH. There was also an association between severe PAH and severe lung disease, on the basis of the fact that previous high-frequency ventilation, prolonged mechanical ventilation, and tracheostomy were more prevalent among patients with severe PAH than among those without severe PAH. However, it is not clear whether this association is an indication of increased PAH among patients with severe BPD or vice versa.

Appropriate screening guidelines for PAH in premature infants do not currently exist, which may have important clinical implications, such as missed or delayed diagnoses. In this study, for example, 4 patients were diagnosed as having PAH at >1 year of age, including 2 with severe PAH. Development of a suitable screening strategy is complicated by a lack of information about the true prevalence of PAH in patients with BPD and uncertainty about the optimal methods of and criteria for screening. Electrocardiography may reveal evidence of RV hypertrophy in many patients with RV hypertension. However, a recent study found that electrocardiography had a sensitivity of only 67% and a positive predictive value of 69% for detecting echocardiographically documented RV hypertrophy in children undergoing evaluation for PAH.[31] These findings mirror our own clinical experience and suggest that electrocardiography alone is insufficient to screen for PAH in infants with BPD. Echocardiography also has limitations as a screening strategy for PAH in this population. In the absence of tricuspid regurgitation, a subjective estimation of septal flattening is the only method of determining RV pressure elevation. Unsedated imaging of active infants may limit the extent and validity of data that can be acquired, whereas sedation of infants with underlying BPD has attendant risks (albeit small).

Indications to screen for PAH in infants with BPD may include evaluation before attempted weaning from oxygen supplementation or assessment of the need for additional prophylaxis against respiratory syncytial virus. Many premature infants do not qualify for a second season of palivizumab in the absence of associated cardiac disease.[32,33] Among all forms of congenital cardiovascular disease, PAH is associated with the most significant risk of morbidity resulting from respiratory syncytial virus infection.[33–35]

Our current approach is to recommend echocardiographic screening for PAH in premature infants with BPD who meet any of the following criteria: (1) extreme prematurity (gestational age at birth of ≤25 weeks or birth weight of ≤600 g), (2) SGA, (3) requirement for prolonged mechanical ventilatory support (duration depends on age), (4) oxygen requirement out of proportion to the severity of lung disease, or (5) persistent poor growth despite adequate caloric intake. For patients born at <28 weeks of gestation or with a birth weight of <1000 g, for whom we estimate the risk of severe PAH to be lower, a screening electrocardiogram may be more cost-effective, despite the limitations described earlier. Cardiac catheterization is typically reserved for patients with severe respiratory disease and severe PAH on echocardiograms or for patients with known or suspected cardiovascular anomalies that may require additional evaluation. Prospective studies to determine risk factors for PAH among infants with BPD are needed to develop more-sensitive and more-specific screening guidelines.

Treatment of PAH in Infants and Children With BPD

The goal of therapy for PAH in children with BPD depends on the severity of the disease. For patients with severe PAH, acute treatment is aimed at increasing the chances of survival and must work in concert with respiratory support. The objectives of therapy for patients with less-severe PAH and those who are recovering from severe disease include minimizing exacerbation and morbidity while supporting pulmonary growth and development of the child. Ultimately, pulmonary growth may be the definitive remedy for BPD-associated PAH.

Appropriate therapy includes excluding causes of prolonged or intermittent hypoxemia other than underlying BPD in this population. Overnight oximetry studies may help diagnose hypoxic episodes, and a sleep study or pneumogram can determine whether hypoxia is attrib-

utable to central, obstructive, or mixed apnea, which may be treated by means other than supplemental oxygen therapy.

Long-term supplemental oxygen therapy is considered the standard treatment for PAH associated with BPD.[3] Concerns about the adverse effects of supplemental oxygen treatment have complicated the issue and may prompt accelerated removal of oxygen therapy. Target systemic arterial oxygen saturations in premature infants remain controversial, but we recommend saturations of >93% for all premature infants and >95% for infants with documented PAH. Data showing persistent elevation of PA pressure beyond infancy and early childhood in formerly premature infants with BPD,[6,24] along with pulmonary vascular responsiveness to low doses of oxygen, support maintaining supplemental oxygen therapy for infants and children with BPD and PAH. For patients with a history of PAH, removal of oxygen should be gradual and should be completed only after an overnight oximetry study confirms that saturations can be maintained above target levels. RV pressure should be monitored with serial echocardiography until it has normalized and remained so for several months after supplemental oxygen therapy has been removed and until the patient has demonstrated an ability to maintain normal oxygen saturation without supplemental oxygen. Reactivity to inhaled NO in this and previous studies suggests the use of NO in an acute setting, a recommendation that may be supported by recent studies suggesting a beneficial effect of NO on neurodevelopmental outcomes for premature infants.[36] Improved pulmonary hemodynamic features in response to inhaled NO also provide an impetus to study the utility of mechanistically similar enteral agents, such as sildenafil.

Limitations

This study is limited by its retrospective design. All patients with BPD at our institution did not undergo echocardiography during the study period, and it is likely that patients with milder elevations in RV pressure did not receive diagnoses, particularly patients whose primary follow-up care was outside our system. Because premature infants with severe lung disease are at risk for death resulting from a variety of conditions, it is possible that patients with severe PAH and severe lung disease were not ascertained if they died as a result of respiratory disease, infection, and/or other factors. Similarly, the frequent association between severe lung disease and severe PAH complicates the assessment of the relationship between PAH severity and survival rates, and our cohort might not have been sufficiently powered to identify independent survival effects of these 2 factors.

CONCLUSIONS

The mortality rate associated with PAH in formerly premature infants with BPD is high. Although risk factors for PAH among infants with BPD are not well defined, premature infants who were SGA at birth were disproportionately represented among our cohort of patients with severe PAH, which supports the hypothesis that SGA status may predispose infants with BPD to PAH. Similarly, there seemed to be an association between severe PAH and more-severe lung disease, although severe PAH was associated with worse survival rates even when analyses were controlled for the severity of BPD. Additional studies are needed to determine risk factors for PAH among infants with BPD and to formulate effective screening strategies and treatment protocols.

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POLAR BEARS?!

"Van Jones is a rare bird. He's a black social activist in Oakland, CA, and as green an environmentalist as they come. He really gets passionate, and funny, when he talks about what it's like to be black and green: 'Try this experiment. Go knock on someone's door in West Oakland, Watts or Newark and say: "We gotta really big problem!" They say: "We do? We do?" "Yeah, we gotta really big problem!" "We do? We do?" "Yeah, we gotta save the polar bears! You may not make it out of this neighborhood alive, but we gotta save the polar bears!"' Mr. Jones then just shakes his head. You try that approach on people without jobs who live in neighborhoods where they've got a lot better chance of getting killed by a passing shooter than a melting glacier, you're going to get nowhere—and without bringing America's underclass into the green movement, it's going to get nowhere, too. 'We need a different on-ramp' for people from disadvantaged communities, says Mr. Jones."

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