ORIGINAL ARTICLE

Cardiac Magnetic Resonance Imaging Evaluation of Neonatal Bronchopulmonary Dysplasia–associated Pulmonary Hypertension

Paul J. Critser^{1,2}, Nara S. Higano^{1,3}, Jean A. Tkach⁴, Emilia S. Olson^{1,4}, David R. Spielberg^{5,6}, Paul S. Kingma^{7,8}, Robert J. Fleck^{4,8}, Sean M. Lang^{2,8}, Ryan A. Moore^{2,8}, Michael D. Taylor^{2,8}, and Jason C. Woods^{1,3,8}

¹Center for Pulmonary Imaging Research, ²Division of Cardiology, ³Division of Pulmonary Medicine, ⁴Department of Radiology, and ⁷Division of Neonatology and Pulmonary Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; ⁵Department of Pediatrics, Baylor College of Medicine, Houston, Texas; ⁶Pulmonary Medicine Service, Texas Children's Hospital, Houston, Texas; and ⁸Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio

Abstract

Rationale: Patients with bronchopulmonary dysplasia (BPD)-associated pulmonary hypertension (PH) have increased morbidity and mortality. Noninvasive assessment relies on echocardiograms (echos), which are technically challenging in this population. Improved assessment could augment decisions regarding PH therapies.

Objectives: We hypothesized that neonatal cardiac magnetic resonance imaging (MRI) will correlate with BPD severity and predict short-term clinical outcomes, including need for PH therapies for infants with BPD.

Methods: A total of 52 infants (31 severe BPD, 9 moderate BPD, and 12 with either mild or no BPD) were imaged between 39 and 47 weeks postmenstrual age on a neonatal-sized, neonatal ICU-sited 1.5-T magnetic resonance (MR) scanner. MR left ventricular eccentricity index (EI), main pulmonary artery-to-aorta (PA/AO) diameter ratio, and pulmonary arterial blood flow were determined. Echos obtained for clinical indications were reviewed. MRI and echo indices were compared with BPD severity and clinical outcomes, including length of stay (LOS), duration of respiratory support, respiratory support at discharge, and PH therapy.

Measurements and Main Results: PA/AO ratio increased with BPD severity. Increased PA/AO ratio, MR-EI, and echo-EIs were associated with increased LOS and duration of respiratory support. No correlation was seen between pulmonary arterial blood flow and BPD outcomes. Controlling for gestational age, birth weight, and

BPD severity, MR-EI was associated with LOS and duration of respiratory support. Increased PA/AO ratio and MR-EI were associated with PH therapy during hospitalization and at discharge.

Conclusions: MRI can provide important image-based measures of cardiac morphology that relate to disease severity and clinical outcomes in neonates with BPD.

Keywords: bronchopulmonary dysplasia; cardiac magnetic resonance imaging; neonatal lung disease; pulmonary hypertension; outcome prediction modeling

At a Glance Commentary

Scientific Knowledge on the Subject: Bronchopulmonary dysplasia (BPD)-associated pulmonary hypertension is associated with increased morbidity and mortality. Current quantitative noninvasive assessment has yielded mixed ability to accurately assess disease severity and predict clinical outcomes.

What This Study Adds to the Field: This study provides the first comprehensive cardiac magnetic resonance imaging assessment in neonatal patients with BPD and BPD-associated pulmonary hypertension. It demonstrates that magnetic resonance imaging can predict short-term clinical outcomes and need for pulmonary vasodilator therapy in infants with BPD better than echocardiography or other clinical measures.

(Received in original form April 17, 2019; accepted in final form September 19, 2019)

N.S.H. was supported by NIH grant T32 HL007752. J.A.T. and M.D.T. were supported by Cincinnati Children's Hospital Medical Center Research Innovation and Pilot Fund.

Author Contributions: P.J.C., N.S.H., D.R.S., S.M.L., and J.C.W. contributed to the experimental design, data analysis, drafting, and revision of the work. J.A.T., E.S.O., P.S.K., R.J.F., R.A.M., and M.D.T. contributed to the experimental design, data analysis, and revision of the work.

Correspondence and requests for reprints should be addressed to Jason C. Woods, Ph.D., Cincinnati Children's Hospital, 3333 Burnet Avenue, ML 5033, Cincinnati, OH 45229. E-mail: jason.woods@cchmc.org.

Am J Respir Crit Care Med Vol 201, Iss 1, pp 73–82, Jan 1, 2020

Copyright © 2020 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201904-0826OC on September 20, 2019

Internet address: www.atsjournals.org

As survival of extremely low gestational age (GA) neonates has increased, so has the incidence of chronic lung disease of prematurity or bronchopulmonary dysplasia (BPD), which remains a significant cause of morbidity and mortality (1–3). BPD is associated with pulmonary vascular disease (PVD) and pulmonary hypertension (PH) due to alteration in development of pulmonary parenchyma and vasculature (2, 4, 5), and due to postnatal episodes of hypoxia or hypercarbia (5). Patients with BPD-associated PVD and PH have worse outcomes with increased duration of respiratory support (5–7), incidence of late respiratory disease (2), and mortality (5–10).

Evaluation of PH in infants with BPD has been limited due to the invasive nature of cardiac catheterization, which is the current gold standard for diagnosis of PH. Alternative noninvasive screening and diagnosis using echocardiography is the standard for this high-risk patient population (11). However, echocardiography is technically limited in infants with BPD due to lung hyperinflation, cardiac malposition, and poor imaging windows (12, 13). Features suggestive of PH include quantitative measures such as tricuspid regurgitation jet velocity (TRJV), tricuspid annular plane systolic excursion (TAPSE), myocardial performance index, and qualitative findings of right atrial enlargement, right ventricular (RV) hypertrophy, RV dilation, and septal flattening. Although estimating RV systolic pressure via TRJV has been the most frequently used quantitative metric, it is reported in a minority of patients with BPD (6, 8); further septal flattening, which is the most sensitive qualitative measure, is subject to interobserver variability (4). These technical limitations of echocardiography have resulted in underdiagnosis or misdiagnosis of some infants with BPD-associated PH. Cardiac catheterization is still required when diagnostic uncertainty persists or escalation of PH therapy is required (4, 11, 12).

Improvement in noninvasive characterization of PH in infants with BPD could improve decisions regarding PH therapies and provide better prognostic information. Magnetic resonance imaging (MRI) is an emerging, noninvasive modality in evaluating chronic lung disease in infants and offers the potential for concurrent assessment of the cardiac phenotype in these patients (14). Dedicated neonatal ICU

(NICU) magnets, faster pulse sequences, and/or small coils have been useful in addressing challenges associated with infant transport and scan length. It is now possible to image neonates without sedation (15–20), and studies have demonstrated that MRI can quantitatively assess lung parenchyma in infants with BPD and predict short-term respiratory outcomes (19, 21). Although cardiac MRI has been used to evaluate PH in adult and older pediatric populations (22–26), no studies have yet been performed to evaluate whether MRI can be used to evaluate PH in neonates.

The current study sought to describe the cardiopulmonary phenotype in neonates with BPD based on MRI and determine MRI and echocardiogram (echo) indices associated with PH. We hypothesized that neonatal cardiac MRI could predict length of stay (LOS), degree of respiratory support, and need for PH-associated therapies for infants diagnosed with BPD. Some of the results of these studies have been previously reported in the form of an abstract (27).

Methods

Study Subjects

Subjects were enrolled with approval of the Institutional Review Board and informed parental consent. Inclusion criteria for patients with BPD consisted of BPD diagnosis according to the 2001 National Institute of Child Health and Human Development/NHLBI consensus definition (28) and 48 weeks or less postmenstrual age (PMA) at MRI. Inclusion criteria for control patients consisted of full-term birth (≥ 37 -wk GA) or preterm birth without BPD, no clinically significant lung disease, and 48 weeks or less PMA at MRI. Exclusion criteria for BPD and control patients included evidence of significant congenital malformations or significant genetic abnormalities, evidence of any respiratory infection at the time of MRI, and standard MRI exclusion criteria.

The study cohort consisted of 52 neonates with a distribution of BPD severity consistent with our NICU population: 31 with severe BPD, 9 with moderate BPD, 4 with mild BPD, 4 preterm control subjects without BPD, and 4 term control subjects who were primarily diagnosed with neurologic or gastrointestinal issues.

As previously described, all subjects were free-breathing and nonsedated, unless

respiratory support or sedation was part of their clinical care at the time of MRI (18, 21). NICU staff monitored all subjects' vital signs during the imaging study. No patient received contrast agent.

MRI Protocol

Neonatal research MRI acquisitions were conducted using a 1.5-T scanner (marketed as an orthopedic scanner by ONI Medical Systems; currently GE Healthcare) located in the NICU (18).

Three MRI sequences were used for cardiac analysis: a short-axis, retrospective ECG-gated, balanced steady-state free-precession imaging acquisition; an axial, ECG-triggered, double inversion-recovery fast spin-echo (FSE) acquisition; and a retrospective ECG-gated velocity-encoded phase contrast cine acquisition perpendicular to the main, right, and left pulmonary arteries, independently. Typical short-axis, steady-state free-precession acquisition parameters were echo time (TE) = 1.6 ms, repetition time (TR) = 3.7 ms, flip angle (FA) = 45°, field of view (FOV) 28–32 cm, pixel resolution 1.09–1.25 mm, slice thickness = 5–6 mm, number of averages = 3, and scan time = 2 minutes. Typical FSE acquisition parameters were TE = 43.0 ms, TR = 736.2 ms, FA = 90°, FOV 16–17 cm, pixel resolution 0.63–0.66 mm, slice thickness = 4 mm, number of averages = 3, and scan time = 3 minutes. Phase contrast cine acquisition parameters were TE = 4.8 ms, TR = 12.6 ms, FA = 20°, velocity encoding of 150–200 cm/s, FOV = 24 cm, pixel resolution = 0.94 mm, slice thickness = 5 mm, number of averages = 3, and scan time = 1 minute.

MRI Analysis

Representative cardiac images with measurements are shown in Figure 1. Diameters of the main pulmonary artery and ascending aorta were measured at the level of the pulmonary artery bifurcation to determine the pulmonary artery-to-aorta (PA/AO) ratio from double inversion-recovery FSE axial stack. PA/AO ratio was investigated as a continuous and categorical variable using thresholds for patients who were normal (≤ 1.09) and patients with PH (≥ 1.3), as previously described (29, 30), with 1.1–1.29 being indeterminate. Left ventricular eccentricity index (LVEI) was measured at end-systole and end-diastole from the short-axis stack. LVEI was

Figure 1. Representative cardiac magnetic resonance images from (A–C) control infants and (D–F) infants with moderate bronchopulmonary dysplasia, demonstrating measurement of (A and D) magnetic resonance eccentricity indexes, (B and E) PA/AO ratio, and (C and F) pulmonary blood flow. AO = aorta; PA = pulmonary artery; RPA = right pulmonary artery.

investigated as a continuous and categorical variable using thresholds for PH (≥ 1.3), as previously described (31–33).

Postprocessing was completed with cvi42 (Circle Cardiovascular Imaging). The right and left ventricles were contoured throughout the cardiac cycle in the short-axis stack, and RV end-systolic volume, RV end-diastolic volume, left ventricular (LV) end-systolic volume, LV end-diastolic volume, stroke volume, LV ejection fraction (LVEF) and RV ejection fraction (RVEF), and cardiac index (CI) were determined. Pulmonary blood flow (PBF) was determined from phase contrast cine for the main pulmonary artery and the sum of left and right pulmonary artery, indexed to body surface area.

Echocardiography

Echos performed for clinical indications were reviewed. Qualitative and quantitative echocardiographic variables of RV size and function, LV size and function, and septal position were assessed. RV systolic pressure was estimated from TRJV measured in parasternal short-axis or apical four-chamber views or via the patent ductus arteriosus (PDA) gradient. TAPSE was measured from M-mode at the lateral tricuspid valve annulus from the apical four-chamber view. LV eccentricity indices were measured at the midventricular level in parasternal short-axis views at end-systole. As previously described,

patients were considered to have echocardiographic evidence of PH (echo-PH) if one of following was present on echo: RV pressure >40 mm Hg by TRJV, RV pressure/systemic systolic pressure >0.5 , intracardiac shunt with bidirectional or right-to-left flow, or any degree of septal flattening (2).

Statistical Analysis

Univariate ANOVA tests were used to assess group differences in MRI and echocardiographic indices, birth weight, and GA for eight outcomes: 1) BPD severity levels (mild, moderate, or severe), 2) degree of respiratory support at NICU discharge (room air, noninvasive oxygen [including nasal cannula or high-flow nasal cannula], ventilator, or death), 3) degree of respiratory support at hospital discharge (room air, noninvasive oxygen, or ventilator), 4) length of hospital stay, 5) duration of ventilator support, 6) duration of any positive-pressure ventilation (PPV; ventilator or noninvasive pressure), 7) duration of any support (ventilator, noninvasive pressure, or oxygen), and 8) pulmonary vasodilator therapy during hospitalization and at discharge. Mean and SD are reported for parametric group data and mean and interquartile range for nonparametric group data.

Multivariable linear regression models were used to investigate four

continuous outcomes: 1) LOS, 2) duration of ventilator support, 3) duration of any PPV, and 4) duration of any support (ventilator, noninvasive pressure, or oxygen). Models were developed for continuous and categorical predictor variables: PA/AO ratio, MR-EI (MR left-ventricular eccentricity index) at end-systole (MR-EIs), dichotomized echo evidence of PH (present/absent), GA, birth weight, and BPD severity. All variables were included in the model independent of their significance. All analyses were performed in SAS 9.3 (SAS Institute Inc.).

Results

Patient demographics are shown in Table 1. MRI was completed in all patients without adverse events. Image quality allowed for measurable PA/AO ratio in 51 (98%), MR-eccentricity index (EI) in 48 (92%), and PBF in 45 (86%) patients. MRI-derived RV end-systolic volume, RV end-diastolic volume, LV end-systolic volume, LV end-diastolic volume, RVEF, LVEF, and CI did not vary significantly between BPD severity groups (Table 2).

Echos were available for review in 43 of 52 patients. The time between echos and MRI studies was 13.98 (2.00–16.25) days. A PDA or ventricular septal defect shunt gradient was present in 8 (19%), TRJV was measureable in 10 (23%), TAPSE was measureable in 30 (70%), and EI was measureable in 42 (98%) patients. Echocardiographic evidence of PH was present in 21 (48%) patients. Echo-derived LVEF did not vary significantly between BPD severity groups (see Table 2). A moderate PDA was seen in 1 patient with moderate BPD, a small PDA was seen in 8 patients (3 with moderate and 5 with severe BPD), patent foramen ovale was seen in 8 patients (1 with mild, 2 with moderate, and 5 with severe BPD), small secundum atrial septal defect was seen in 1 patient with moderate BPD, and tiny apical muscular ventricular septal defect was seen in 1 patient with moderate BPD. Two patients required PDA closure; the remainder had spontaneous closure of their PDA.

Control infants and infants with mild BPD were combined for the analysis because MRI indices were not significantly different, and none required respiratory support at discharge or received pulmonary vasodilator therapy.

Table 1. Demographic Data for the Cohort, Separated by NICHD Bronchopulmonary Dysplasia Severity

	Control or Mild BPD	Moderate BPD	Severe BPD	P Value
<i>n</i>	12	9	31	
Birth weight, g	1,996 ± 877	893 ± 219	729 ± 307	0.004
Birth weight for gestational age, percentile	44.4 ± 24.5	52.78 ± 26.4	35.10 ± 31.90	0.26
Gestational age, wk	33.8 ± 5.2	26.6 ± 1.8	25.9 ± 2.1	0.04
Sex, M/F, %	58/42	33/67	48/52	—
Twin gestation, %	25	22	45	—
Mechanical ventilation at 7 d of life, <i>n</i> (%)	2 (16.7)	6 (66.7)	26 (83.9)	—
Tracheostomy, <i>n</i> (%)	0 (0)	1 (11.1)	18 (58.1)	—
Respiratory support at discharge				
None, <i>n</i> (%)	12 (100)	5 (55.6)	2 (6.5)	—
Oxygen, <i>n</i> (%)	0 (0)	3 (33.3)	9 (29.0)	—
Ventilator, <i>n</i> (%)	0 (0)	1 (11.1)	18 (58.1)	—
Death, <i>n</i> (%)	0 (0)	0 (0)	3 (9.7)	—
Length of stay				
NICU, d	62.6 ± 51.2	108.9 ± 38.5	188.1 ± 46.8	<0.001
Hospital, d	70.2 ± 53.4	135.7 ± 110.9	254.8 ± 130.9	<0.001
Pulmonary vasodilator therapy, <i>n</i> (%)				
During hospitalization	0 (0)	0 (0)	18 (58)	—
Hospital discharge	0 (0)	0 (0)	10 (32)	—
Sildenafil	0 (0)	0 (0)	10 (32)	—
Bosentan	0 (0)	0 (0)	2 (6)	—

Definition of abbreviations: BPD = bronchopulmonary dysplasia; NICU = neonatal ICU; NICHD = National Institute of Child Health and Human Development.

Values are mean ± SD unless otherwise indicated.

In the 21 patients with echo-PH, MR-EI was significantly increased compared with patients without echo-PH (1.23 ± 0.22 vs. 1.1 ± 0.10 , respectively; $P = 0.0224$). Additional MRI indices, including PA/AO

ratio, CI, PBF, RV end-systolic volume, RV end-diastolic volume, and MR RVEF, were not significantly different between patients with echo-PH and without echo-PH.

BPD severity (Figure 2) correlated with birth weight, GA, and PA/AO ratio. PA/AO ratio was significantly increased in patients with severe BPD compared with moderate BPD, mild BPD, and control

Table 2. Echocardiogram and Magnetic Resonance Imaging Indices for Control Subjects and Infants with Mild, Moderate, or Severe Bronchopulmonary Dysplasia

	<i>n</i>	Control or Mild BPD	Moderate BPD	Severe BPD	P Value
Echo					
TAPSE, cm	30	1.30	1.37 (1.28–1.45)	1.04 (0.9–1.2)	—
LVEIs	42	1.10 (0.97–1.18)	1.25 (1.06–1.31)	1.22 (1.05–1.32)	0.694
LVEId	42	1.19 (1.02–1.25)	1.12 (1.01–1.13)	1.10 (1.00–1.21)	0.615
LVEF, %	43	63.1 (58.9–70.2)	66.5 (63.0–71.0)	61.7 (57.3–64.6)	0.135
MRI					
cGA, wk	52	33.7 (27.7–37.7)	26.6 (25.2–27.9)	25.9 (24.4–26.7)	0.0001
PA/AO ratio	51	1.00 (0.93–1.12)	1.06 (0.98–1.05)	1.19 (1.02–1.31)	0.036
LVEIs	48	1.09 (1.01–1.14)	1.11 (1.00–1.19)	1.18 (1.06–1.26)	0.228
LVEId	48	1.13 (1.10–1.16)	1.16 (1.05–1.23)	1.19 (1.09–1.31)	0.558
PBF, L/min/m ²	45	4.2 (3.9–4.5)	4.6 (3.4–5.5)	4.2 (3.5–4.9)	0.630
RVEDVi, ml/m ²	46	42.0 (34.6–46.1)	39.3 (31.3–45.7)	40.8 (32.6–46.2)	0.888
RVESVi, ml/m ²	46	16.3 (12.9–19.9)	14.0 (10.1–17.3)	17.4 (14.0–20.0)	0.256
RVEF, %	46	60.5 (57.5–63.5)	63.7 (56.5–74.2)	58.4 (55.0–64.9)	0.214
LVEDVi, ml/m ²	46	39.9 (35.8–41.9)	47.7 (40.4–50.2)	41.3 (35.9–42.1)	0.219
LVESVi, ml/m ²	46	14.2 (12.9–15.4)	18.2 (13.4–25.1)	16.5 (13.1–20.1)	0.376
LVEF, %	46	64.1 (57.0–67.1)	62.2 (58.5–64.4)	60.8 (55.5–64.6)	0.344
CI, L/min/m ²	46	3.8 (3.3–4.3)	5.4 (4.1–6.0)	3.9 (3.2–4.5)	0.093

Definition of abbreviations: AO = aorta; BPD = bronchopulmonary dysplasia; cGA = corrected gestational age at time of magnetic resonance imaging; CI = cardiac index; echo = echocardiogram; LVEDVi = left ventricular end-diastolic volume indexed to body surface area; LVEF = left ventricular ejection fraction; LVEId = left ventricular eccentric index at end diastole; LVEIs = left ventricular eccentricity index at end systole; LVESVi = left ventricular end-systolic volume indexed to body surface area; MRI = magnetic resonance imaging; PA = pulmonary artery; PBF = pulmonary blood flow; RVEF = right ventricular ejection fraction; RVEDVi = right ventricular end-diastolic volume indexed to body surface area; RVESVi = right ventricular end-systolic volume indexed to body surface area; TAPSE = tricuspid annular plane systolic excursion.

Values are median (interquartile range). PA/AO ratio was associated with BPD severity ($P < 0.05$).

Figure 2. Clinical BPD severity was inversely correlated with (A) birth weight ($P=0.004$) and (B) gestational age ($P=0.04$), and was directly correlated with (C) PA/AO ratio ($P=0.036$). Box plot bars are median and interquartile range, circles are mean, and whiskers are 9th to 91st percentile. AO = aorta; BPD = bronchopulmonary dysplasia; PA = pulmonary artery.

patients ($P=0.036$). MR-EI, CI, PBF, ejection fraction, ventricular volumes, and echo indices did not correlate with BPD severity.

Respiratory support at discharge from the NICU and hospital were correlated with birth weight, PA/AO ratio, and MR-EIs (Figure 3). PA/AO ratio was significantly increased in patients who died compared with patients discharged on ventilator support, supplemental oxygen, and no respiratory support ($P=0.003$). MR-EIs were significantly increased in patients who died compared with patients discharged on ventilator support, supplemental oxygen, and no respiratory support ($P=0.004$). PBF and echo indices were not significantly correlated with respiratory support at NICU or hospital discharge.

Duration of PPV correlated with PA/AO ratio, MR-EIs, and echo-EIs with an increase of 45, 78, and 45 days for every 0.1 unit increase in each metric, respectively (Figure 4). Patients with echo-PH had increased duration of any PPV compared with patients without echo-PH (235 ± 225 vs. 140 ± 109 d, respectively; $P=0.007$). Similar correlations were seen for durations of ventilator support and supplemental

oxygen (data not shown). Durations of ventilator support, any PPV, and any support were longer for patients with PA/AO ratio ≥ 1.3 , MR-EIs ≥ 1.3 , and echo-EIs ≥ 1.3 compared with patients with PA/AO ratio = 1.1–1.29 or ≤ 1.09 , MR-EIs < 1.3 , and echo-EIs < 1.3 , respectively (Figure 5). Although there was a modest correlation between MR-EIs and echo-EIs ($R^2=0.3$), MR-EIs was a stronger predictor than echo-EIs, for each of the respiratory support categories (e.g., for duration of ventilator support, MR-EIs $R^2=0.52$ vs. echo-EIs $R^2=0.27$, respectively).

NICU and hospital LOS were longer for patients with PA/AO ratio ≥ 1.3 , MR-EIs ≥ 1.3 , and with echo-PH. LOS was longer for patients with PA/AO ratio ≥ 1.3 (214 ± 56 and 328 ± 176 d for NICU and hospital LOS, respectively) compared with patients with PA/AO ratio = 1.1–1.29 (143 ± 59 d [$P=0.002$] and 159 ± 70 d [$P=0.005$], respectively) and patients with PA/AO ratio ≤ 1.09 (130 ± 68 d [$P=0.009$] and 168 ± 125 d [$P=0.004$], respectively), for patients with MR-EIs ≥ 1.3 (202 ± 22 and 372 ± 195 d, respectively) compared with patients with

MR-EIs < 1.3 (135 ± 74 d [$P=0.032$] and 154 ± 97 d [$P<0.001$], respectively), and for patients with echo-PH (188 ± 40 and 278 ± 153 d) compared with patients without echo-PH (148 ± 69 d [$P=0.029$] and 172 ± 89 d [$P=0.01$], respectively). Hospital LOS was longer for patients with echo-EIs ≥ 1.3 compared with patients with echo-EIs < 1.3 (317 ± 200 vs. 194 ± 90 d, respectively; $P=0.006$).

Including all variables in the multivariable analysis, MR-EIs were significantly associated with clinical outcomes. Hospital LOS increased 79 days for every 0.1 unit increase in MR-EIs ($P=0.004$). Duration of respiratory support was increased for patients with MR-EIs ≥ 1.3 compared with patients with MR-EIs < 1.3 with an increased duration of ventilator support of 442 days ($P=0.003$), total PPV of 418 days ($P=0.002$), and supplemental oxygen of 359 days ($P=0.006$). BPD severity was significantly associated with duration of total PPV, but echo-PH and PA/AO ratio were not significantly associated with any of the clinical outcomes in the multivariable model (Table 3).

Ten patients were discharged from the hospital on pulmonary vasodilator therapy.

Figure 3. Cardiac magnetic resonance imaging indices and birth weight are each correlated with respiratory support at neonatal ICU (NICU) and hospital discharge, and are categorized as none, supplemental oxygen, ventilator, or death. (A and D) PA/AO ratio and (B and E) MR-EIs had a direct relationship with respiratory support at NICU and hospital discharge. Birth weight had an inverse relationship with respiratory support at (C and F) NICU and hospital discharge, respectively. Box plot bars are median and interquartile range, circles are mean, and whiskers are 9th to 91st percentile. AO = aorta; MR-EIs = magnetic resonance eccentricity indexes; PA = pulmonary artery.

An additional eight patients received pulmonary vasodilator therapy while in the hospital but not at discharge. Patients who were discharged on PH therapy had

increased PA/AO ratio ($P=0.001$) and MR-EIs ($P<0.001$) compared with those who received PH therapy in the hospital but not at discharge, and compared with

those who never received PH therapy (Figure 6). Dichotomizing PA/AO ratio and MR-EIs based on previously described thresholds yields similar results. Individual

Figure 4. Duration of ventilator support (total PPV) was correlated with (A) PA/AO ratio ($R^2=0.18$; $P=0.002$), (B) MR-EIs ($R^2=0.35$; $P<0.001$), and (C) echo-EIs ($R^2=0.38$; $P<0.001$). Dashed line is 95% confidence interval around the linear fit. AO = aorta; Echo-EIs = echocardiogram–eccentricity indexes; MR-EIs = magnetic resonance eccentricity indexes; PA = pulmonary artery; PPV = positive-pressure ventilation.

echo indices were not significantly correlated with PH therapy. Echo-PH was seen in 90% of patients discharged on PH therapy, 63% of patients who received PH therapy in the hospital but not at discharge, and 21% of patients who never received PH therapy.

Discussion

In this first study of cardiac MRI assessment of infant BPD, 52 patients underwent MRI between 39 and 47 weeks PMA to assess the cardiac phenotype. The majority of patients had quantitative MRI assessment, with measurable PA/AO ratio in 51 (98%), MR-EI in 48 (92%), and PBF in 45 (86%) patients. In contrast, a minority of patients

had quantitative echo findings of PH, with <25% having a sufficient TRJV or intracardiac shunt gradient to estimate RV systolic pressure; this is consistent with prior reports (6, 8). Importantly, in a multivariable model including GA, birth weight, BPD severity, and imaging indices (PA/AO ratio, MR-EIs, and echo-PH), MR-EIs was the most significant variable in the model and was associated with hospital LOS and duration of all forms of respiratory support.

Similar to prior reports, perinatal risk factors, including GA and birth weight, were associated with BPD severity (34), and BPD severity correlated with outcomes including increased LOS, duration of mechanical ventilation, and need for supplemental oxygen at discharge. PA/AO ratio was the

only imaging index associated with BPD severity, with PA/AO ratio significantly increased with patients with increasing BPD severity. The lack of correlation of other imaging indices, including CI, with BPD severity likely reflects the heterogeneity of the BPD population because prior reports have demonstrated only a subset have PVD and PH (5, 6, 8). It may also be related to inherent inadequacy of the traditional definition of clinical disease severity (3, 35).

PA/AO ratio and MR-EIs were correlated with clinical outcomes including LOS, duration of respiratory support, and level of respiratory support at discharge from the NICU and hospital as both continuous and categorical variables using previously clinically defined thresholds.

Figure 5. (A) Patients with pulmonary artery–to–aorta (PA/AO) ratio ≥ 1.3 (black bars) had longer duration of ventilator support, duration of any positive-pressure ventilation (PPV), and duration of any respiratory support compared with patients with PA/AO ratio 1.1–1.29 (gray bars) and PA/AO ratio ≤ 1.09 (white bars). (B) Patients with magnetic resonance eccentricity indexes (MR-EIs) ≥ 1.3 had longer duration of ventilator support, duration of any PPV support, and duration of any support compared with patients with MR-EIs < 1.3 . (C) Patients with echocardiogram–eccentricity indexes (echo-EIs) ≥ 1.3 had longer duration of ventilator support, duration of any PPV support, and duration of any support compared with patients with echo-EIs < 1.3 . Data are mean $\pm$ SD; * $P<0.05$ and ** $P<0.005$.

Table 3. Multivariable Analysis Demonstrated Correlation of Magnetic Resonance Eccentricity Index with Length of Stay and Duration of Respiratory Support, and Correlation of Bronchopulmonary Dysplasia Severity with Duration of Total Positive-Pressure Ventilation

Outcome	Total R^2 of Model	P Value of Significant Variable(s)	Increase in Duration (d)
Hospital LOS	0.5	MR-EIs: 0.004	79 per 0.1 increase in MR-EIs
Invasive PPV	0.67	MR-EIs ≥ 1.3 : 0.003	442 for MR-EIs ≥ 1.3 vs < 1.3
Total PPV	0.68	MR-EIs ≥ 1.3 : 0.002 BPD severe vs. mild: 0.17 BPD severe vs. moderate: 0.039	418 for MR-EIs ≥ 1.3 vs < 1.3 187 for severe vs. mild BPD 134 for severe vs. moderate
Total PPV + O ₂	0.64	MR-EIs ≥ 1.3 : 0.006	359 for MR-EIs ≥ 1.3 vs. < 1.3

Definition of abbreviations: BPD = bronchopulmonary dysplasia; LOS = length of stay; MR-EI = magnetic resonance eccentricity index; PPV = positive-pressure ventilation.

Analysis was also conducted with threshold values of MR-EIs ≤ 1.09 , 1.1–1.29, and ≥ 1.3 , with similar findings (unreported data). Additionally, echo-EIs were correlated with duration of respiratory support and hospital LOS. In comparison with MR-EIs, increase in echo-EIs was associated with a smaller increase in duration of respiratory support. This is likely due to increased variability in echo-derived EI.

PBF did not significantly correlate with BPD severity or clinical outcomes in this study. However, it did show a (nonsignificant) parabolic relationship with respiratory support at NICU and hospital discharge. It is possible the heterogeneity of pulmonary vascular flow is inadequately captured by aggregate PBF, and further evaluation with more nuanced assessment of the pulmonary vascular tree is required in future studies.

Ten patients (19%) of the population were discharged on pulmonary vasodilatory therapy, with the majority receiving sildenafil monotherapy. All patients discharged on pulmonary vasodilator therapy had severe BPD and represented 32% of the severe BPD population. The incidence of BPD-PH in this report is consistent with prior data. Cohen and colleagues reported 45% of BPD-PH infants were able to wean off sildenafil due to improvement in PH (36). Similarly, in this study, an additional 8 infants received PH therapy during hospitalization but not at discharge, representing 44% of BPD-PH infants.

MR indices PA/AO ratio and MR-EIs were correlated with pulmonary vasodilator therapy both during hospitalization and at discharge. The subset of patients treated in hospital but not at discharge primarily had PA/AO ratio and MR-EIs between 1.0 and 1.3. This correlates with the prior report by Abraham and Weismann that demonstrated qualitative septal flattening with echo-EIs ≥ 1.15 but only demonstrated estimated RV pressure greater than half systemic when echo-EIs were ≥ 1.3 (33). Although this study lacks the hemodynamic data from cardiac catheterization to demonstrate improvement in the RV pressure or pulmonary vascular resistance, these data suggest that patients with intermediate PA/AO ratio and MR-EIs may represent the population of BPD-PH infants who may experience improvement in PH in the short-term compared with those with PA/AO ratio and MR-EIs ≥ 1.3 .

A limitation of this study is the single-center retrospective design with a modest

Figure 6. Pulmonary vasodilatory therapy usage was associated with pulmonary artery-to-aorta (PA/AO) ratio and magnetic resonance eccentricity indexes (MR-EIs). PA/AO ratio ($P = 0.001$) and MR-EIs ($P < 0.001$) were increased in patients who were discharged on therapy compared with those patients who were treated during hospital stay but not at discharge, and who were never treated. Box plot bars are median and interquartile range, circles are mean, and whiskers are 9th to 91st percentile. PH = pulmonary hypertension.

number of neonates. Another limitation is the uneven distribution of clinical BPD severity. The distribution of clinical severity may represent the bias of a primarily referral-based NICU where infants with severe sequelae of prematurity or infants with complex comorbidities are typically admitted. Additionally, eight patients had PDA, patent foramen ovale, or small atrial septal defect, with two patients ultimately undergoing PDA device closure. Although none of these patients had significant chamber dilation or evidence of significant shunting, the presence of a shunt could potentially confound assessment of cardiac morphology. There is also a lack of cardiac MRI data in healthy neonates,

and further work is necessary to describe normative data in this population. Finally, the majority of patients are still infants, and future studies are needed to determine a correlation of imaging indices with long-term clinical outcomes.

In conclusion, this study is the first report to demonstrate the feasibility of MR-based assessment of cardiac morphology and PBF in BPD infants. Importantly, although our studies were performed on a dedicated infant magnet, these same imaging techniques can be applied on standard adult MRI scanners with appropriate patient coils. Further, the MR-based imaging indices PA/AO ratio and MR-EI are useful predictors of short-term clinical outcomes, including

duration of respiratory support, LOS, respiratory support at discharge, and need for pulmonary vasodilator therapy. Specifically, these results indicate that MRI may be useful in determining which neonates warrant early or prolonged pulmonary vasodilator therapy. Performing cardiac MRI assessment of BPD infants in conjunction with emerging pulmonary and airway MRI techniques could provide for potential comprehensive longitudinal imaging evaluation of the complex cardiorespiratory morbidities in this heterogeneous population. ■

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

References

- Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med* 2007;357:1946–1955.
- Mourani PM, Mandell EW, Meier M, Younoszai A, Brinton JT, Wagner BD, et al. Early pulmonary vascular disease in preterm infants is associated with late respiratory outcomes in childhood. *Am J Respir Crit Care Med* 2019;199:1020–1027.
- Higgins RD, Jobe AH, Koso-Thomas M, Bancalari E, Viscardi RM, Hartert TV, et al. Bronchopulmonary dysplasia: executive summary of a workshop. *J Pediatr* 2018;197:300–308.
- Goss KN, Everett AD, Mourani PM, Baker CD, Abman SH. Addressing the challenges of phenotyping pediatric pulmonary vascular disease. *Pulm Circ* 2017;7:7–19.
- Mourani PM, Sontag MK, Younoszai A, Miller JI, Kinsella JP, Baker CD, et al. Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2015;191:87–95.
- An HS, Bae EJ, Kim GB, Kwon BS, Beak JS, Kim EK, et al. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. *Korean Circ J* 2010;40:131–136.
- Lagatta JM, Hysinger EB, Zaniletti I, Wymore EM, Vyas-Read S, Yallapragada S, et al. Children's Hospital Neonatal Consortium Severe BPDFG. The impact of pulmonary hypertension in preterm infants with severe bronchopulmonary dysplasia through 1 year. *J Pediatr* 2018;203:218–224, e3.
- Bhat R, Salas AA, Foster C, Carlo WA, Ambalavanan N. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. *Pediatrics* 2012;129:e682–e689.
- Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro RV, Thomas KC, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. *Pediatrics* 2007;120:1260–1269.
- Mirza H, Ziegler J, Ford S, Padbury J, Tucker R, Laptook A. Pulmonary hypertension in preterm infants: prevalence and association with bronchopulmonary dysplasia. *J Pediatr* 2014;165:909–914, e1.
- Krishnan U, Feinstein JA, Adatia I, Austin ED, Mullen MP, Hopper RK, et al. Evaluation and management of pulmonary hypertension in children with bronchopulmonary dysplasia. *J Pediatr* 2017;188:24–34, e1.
- Mourani PM, Abman SH. Pulmonary hypertension and vascular abnormalities in bronchopulmonary dysplasia. *Clin Perinatol* 2015;42:839–855.
- Carlton EF, Sontag MK, Younoszai A, DiMaria MV, Miller JI, Poindexter BB, et al. Reliability of echocardiographic indicators of pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. *J Pediatr* 2017;186:29–33.
- Walkup LL, Woods JC. Newer imaging techniques for bronchopulmonary dysplasia. *Clin Perinatol* 2015;42:871–887.
- Hahn AD, Higano NS, Walkup LL, Thomen RP, Cao X, Merhar SL, et al. Pulmonary MRI of neonates in the intensive care unit using 3D ultrashort echo time and a small footprint MRI system. *J Magn Reson Imaging* 2017;45:463–471.
- Higano NS, Fleck RJ, Spielberg DR, Walkup LL, Hahn AD, Thomen RP, et al. Quantification of neonatal lung parenchymal density via ultrashort echo time MRI with comparison to CT. *J Magn Reson Imaging* 2017;46:992–1000.
- Higano NS, Hahn AD, Tkach JA, Cao X, Walkup LL, Thomen RP, et al. Retrospective respiratory self-gating and removal of bulk motion in pulmonary UTE MRI of neonates and adults. *Magn Reson Med* 2017;77:1284–1295.
- Tkach JA, Merhar SL, Kline-Fath BM, Pratt RG, Loew WM, Daniels BR, et al. MRI in the neonatal ICU: initial experience using a small-footprint 1.5-T system. *AJR Am J Roentgenol* 2014;202:W95–W105.
- Walkup LL, Tkach JA, Higano NS, Thomen RP, Fain SB, Merhar SL, et al. Quantitative magnetic resonance imaging of bronchopulmonary dysplasia in the neonatal intensive care unit environment. *Am J Respir Crit Care Med* 2015;192:1215–1222.
- Schopper MA, Walkup LL, Tkach JA, Higano NS, Lim FY, Haberman B, et al. Evaluation of neonatal lung volume growth by pulmonary magnetic resonance imaging in patients with congenital diaphragmatic hernia. *J Pediatr* 2017;188:96–102, e1.
- Higano NS, Spielberg DR, Fleck RJ, Schapiro AH, Walkup LL, Hahn AD, et al. Neonatal pulmonary magnetic resonance imaging of bronchopulmonary dysplasia predicts short-term clinical outcomes. *Am J Respir Crit Care Med* 2018;198:1302–1311.
- Friesen RM, Schäfer M, Ivy DD, Abman SH, Stenmark K, Browne LP, et al. Proximal pulmonary vascular stiffness as a prognostic factor in children with pulmonary arterial hypertension. *Eur Heart J Cardiovasc Imaging* 2019;20:209–217.
- Ley S, Mereles D, Puderbach M, Gruenig E, Schöck H, Eichinger M, et al. Value of MR phase-contrast flow measurements for functional assessment of pulmonary arterial hypertension. *Eur Radiol* 2007;17:1892–1897.
- Ley S, Mereles D, Risse F, Grünig E, Ley-Zapozhyan J, Tecer Z, et al. Quantitative 3D pulmonary MR-perfusion in patients with pulmonary arterial hypertension: correlation with invasive pressure measurements. *Eur J Radiol* 2007;61:251–255.
- Schäfer M, Wilson N, Ivy DD, Ing R, Abman S, Browne LP, et al. Noninvasive wave intensity analysis predicts functional worsening in children with pulmonary arterial hypertension. *Am J Physiol Heart Circ Physiol* 2018;315:H968–H977.

26. Skrok J, Shehata ML, Mathai S, Girgis RE, Zaiman A, Mudd JO, *et al.* Pulmonary arterial hypertension: MR imaging-derived first-pass bolus kinetic parameters are biomarkers for pulmonary hemodynamics, cardiac function, and ventricular remodeling. *Radiology* 2012;263:678–687.
27. Critser P, Olsen ED, Tkach JA, Higano NS, Kingma PS, Spielberg DR, *et al.* Cardiac magnetic resonance imaging evaluation of neonatal bronchopulmonary dysplasia associated pulmonary hypertension. Presented at the 12th International Conference Neonatal and Childhood Pulmonary Vascular Disease March 9, 2018, San Francisco, CA. Abstract.
28. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723–1729.
29. Caro-Domínguez P, Compton G, Humpl T, Manson DE. Pulmonary arterial hypertension in children: diagnosis using ratio of main pulmonary artery to ascending aorta diameter as determined by multi-detector computed tomography. *Pediatr Radiol* 2016;46:1378–1383.
30. Compton GL, Florence J, MacDonald C, Yoo SJ, Humpl T, Manson D. Main pulmonary artery-to-ascending aorta diameter ratio in healthy children on MDCT. *AJR Am J Roentgenol* 2015;205:1322–1325.
31. Averin K, Michelfelder E, Sticka J, Cash M, Hirsch R. Changes in ventricular geometry predict severity of right ventricular hypertension. *Pediatr Cardiol* 2016;37:575–581.
32. McCrary AW, Malowitz JR, Hornick CP, Hill KD, Cotten CM, Tatum GH, *et al.* Differences in eccentricity index and systolic-diastolic ratio in extremely low-birth-weight infants with bronchopulmonary dysplasia at risk of pulmonary hypertension. *Am J Perinatol* 2016;33:57–62.
33. Abraham S, Weismann CG. Left ventricular end-systolic eccentricity index for assessment of pulmonary hypertension in infants. *Echocardiography* 2016;33:910–915.
34. Nagiub M, Kanaan U, Simon D, Guglani L. Risk factors for development of pulmonary hypertension in infants with bronchopulmonary dysplasia: systematic review and meta-analysis. *Paediatr Respir Rev* 2017;23:27–32.
35. Jobe AH, Bancalari EH. Controversies about the definition of bronchopulmonary dysplasia at 50 years. *Acta Paediatr* 2017;106:692–693.
36. Cohen JL, Nees SN, Valencia GA, Rosenzweig EB, Krishnan US. Sildenafil use in children with pulmonary hypertension. *J Pediatr* 2019;205:29–34, e1.