Follow-up after Percutaneous Patent Ductus Arteriosus Occlusion in Lower Weight Infants

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Objectives To describe longer term outcomes for infants <6 kg undergoing percutaneous occlusion of the patent ductus arteriosus (PDA).

Study design This was a retrospective cohort study of infants <6 kg who underwent isolated percutaneous closure of the PDA at a single, tertiary center (2003-2017). Cardiopulmonary outcomes and device-related complications (eg, left pulmonary artery obstruction) were examined for differences across weight thresholds (very low weight, <3 kg; low weight, 3-<6 kg). We assessed composite measures of respiratory status during and beyond the initial hospitalization using linear mixed effects models.

Results In this cohort of lower weight infants, 92 of 106 percutaneous occlusion procedures were successful. Median age and weight at procedure were 3.0 months (range, 0.5-11.1 months) and 3.7 kg (range, 1.4-5.9 kg), respectively. Among infants with pulmonary artery obstruction on initial postprocedural echocardiograms (n = 20 [22%]), obstruction persisted through hospital discharge in 3 infants. No measured variables were associated with device-related complications. Rates of oxygenation failure (28% vs 8%; $P < .01$) and decreased left ventricular systolic function (29% vs 5%; $P < .01$) were higher among very low weight than low weight infants. Pulmonary scores decreased (indicating improved respiratory status) following percutaneous PDA closure.

Conclusions Percutaneous PDA occlusion among lower weight infants is associated with potential longer term improvements in respiratory health. Risks of device-related complications and adverse cardiopulmonary outcomes, particularly among very low weight infants, underscore the need for continued device modification. Before widespread use, clinical trials comparing percutaneous occlusion vs alternative treatments are needed. *(J Pediatr 2019;212:144-50)*.

Percutaneous (catheter-based) occlusion of a patent ductus arteriosus (PDA) is the procedure of choice for ductal closure in adults, children, and infants ≥6 kg.[1,2] In these more mature patients, percutaneous occlusion offers several benefits over surgical PDA ligation, including fewer complications, shorter recovery times, and lower health care expenditures.[3,4] However, use among lower weight infants (<6 kg at time of procedure) is not widely accepted, because previous studies have excluded this population, and some manufacturer recommendations specify use in patients >6 kg.[5,6] Although recent investigators have characterized procedural success (feasibility) rates among lower weight infants >90%, outcomes beyond the immediate postprocedural period, including the timing and nature of device-related obstruction (eg, left pulmonary artery obstruction) and cardiopulmonary compromise (eg, decreased myocardial performance) are not well-described.[2,7] Additionally, medium-term and longer term respiratory outcomes, including those beyond the hospitalization, remain largely unknown.

The primary objectives of the present study were to characterize the incidence of and risk factors for device-related obstruction and cardiopulmonary compromise among lower weight infants undergoing percutaneous PDA occlusion. A secondary objective was to compare respiratory status before and after

AVP-II	Amplatzer Vascular Plug-II
DA	Descending aorta
LVEF	Left ventricular ejection fraction
LW	Low weight
PDA	Patent ductus arteriosus
PH	Pulmonary arterial hypertension
VLW	Very low weight

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percutaneous PDA occlusion, including respiratory outcomes beyond the initial hospitalization.

Methods

This retrospective observational cohort study at Nationwide Children's Hospital (NCH; #IRB17-00518) was conducted between January 2003 and February 2017. We included lower weight infants referred for percutaneous PDA closure and with a technically successful percutaneous occlusion, defined as the patient leaving the catheterization laboratory with a device in the PDA. We included only data from infants who underwent successful device placement to describe outcomes and potential complications related to longer term placement of the closure device. Infants referred for percutaneous PDA closure who did not undergo successful device placement (technical failures) were excluded from primary analysis, but data on their outcomes were gathered. Exclusion criteria included prior cardiac catheterization or surgery, a concurrent procedure at the time of PDA closure (eg, atrial septal defect closure), critical congenital heart disease,[8] and a diagnosis limiting longer term survival (eg, trisomy 13).[9] No infant was excluded on the basis of gestational age, illness severity, ductal diameter, or ductal length.

Data collected included birth weight, gestational age at birth, sex, additional cardiac defects (eg, atrial septal defects, ventricular septal defects), diagnosis of bronchopulmonary dysplasia,[10] indications for PDA closure, presence of known genetic or chromosomal syndrome (eg, trisomy 21), age in months at the time of the procedure, and weight at the time of procedure (very low weight [VLW], <3 kg; low weight [LW], 3-<6 kg).

Echocardiograms were performed in accordance with guidelines from the American Society of Echocardiography.[11] When feasible, measurements were obtained in triplicate and averaged. In general, infants referred for percutaneous PDA occlusion had echocardiograms before closure, immediately after closure (<24-48 hours), approximately 1 month after closure, and before hospital discharge. In cases without an echocardiogram at discharge, the latest reported echocardiogram was used. Additional echocardiograms were at the discretion of the attending provider.

To evaluate for device-related complications and cardiopulmonary outcomes, 840 echocardiograms (median 7 per infant; range, 3-17) were independently reviewed. Definitions for adverse cardiopulmonary outcomes and device-related complications were based on previous studies.[12-16] Because composite outcomes are complicated by the magnitude of the risk of the intervention across component end points and by the relative importance of the different components, individual metrics were examined across the 2 weight thresholds.

To evaluate the characteristics of the PDA before ductal occlusion, the shunt pattern was classified as (1) left to right, (2) bidirectional, or (3) right to left. When the pattern was bidirectional, the proportion of the cardiac cycle with right-to-left shunting was measured as the time of right-to-left shunting divided by the total length of the cardiac cycle. Descending aorta (DA) diastolic flow was classified into 3 groups: anterograde throughout diastole, no clear direction to diastolic flow, and retrograde throughout diastole. Left ventricular internal dimension in end-diastole was used as a marker of left ventricular volume loading.[17]

Procedural details (eg, case duration, type of device) and adverse events during the procedure were abstracted. Although use of heparin (timing, dose) was at the discretion of the attending interventional cardiologist, our institutional approach was to administer an initial bolus of 100 U/kg of unfractionated heparin, unless contraindicated. Additional bolus doses were provided to maintain an activated clotting time of >250 s. The definition of pulmonary arterial hypertension (PH) was based on a mean pulmonary artery pressure of >25 mm Hg with cardiac catheterization under baseline conditions.[18]

The primary goal of the study was to evaluate outcomes beyond the catheterization, but immediate procedural details were examined to provide a comprehensive risk/benefit profile of the procedure. When multiple device placements were attempted, only the final implant was recorded. Immediate procedural adverse events were stratified according to severity level (1-5).[19,20] Based on previous studies suggesting differences in complication rates among infants with long tubular ducts (type C) compared with other morphologies,[7] type C PDAs were compared with other PDA classifications according to standard angiographic criteria.[21] Based on studies suggesting a higher risk profile for the Amplatzer Vascular Plug II (AVP-II; Abbott, Lake Bluff, IL) device,[7] the Amplatzer Vascular Plug II was compared with other PDA closure devices. The definitions for adverse cardiopulmonary outcomes and device related outcomes are included in **Appendix** (available at www.jpeds.com).

Pulmonary outcomes were quantified using a composite pulmonary score based on weighted clinical therapies, including type of respiratory support (mechanical ventilation, continuous positive airway pressure, or nasal cannula), need for supplemental oxygen, and pulmonary medications (systemic steroids, diuretics).[22] Over time, lower pulmonary scores reflect improving respiratory status. Pulmonary scores were calculated on a weekly basis 4 weeks before the procedure and up to 28 weeks after the procedure. Follow-up beyond the initial hospitalization included outpatient imaging (echocardiogram, ventilation/perfusion scan), clinic documentation (eg, differences in upper/lower extremity blood pressure gradients, PH medications), and causes of death, if applicable.

Statistical Analyses

Variables are presented as means ± standard deviations or medians with range. Characteristics of infants who did and did not experience any device-related complication (composite), were compared using unpaired *t* tests or Wilcoxon rank-sum tests for continuous variables and χ^2 or Fisher exact tests for categorical variables; similar comparisons were made for VLW infants vs LW infants and infants with

PH vs infants without PH. Additionally, the timing of the postnatal echocardiogram among infants with vs without postligation cardiac syndrome was assessed. To evaluate whether procedural weight and age modified each other's effects on the risk of a device-related complication, we fit a multivariable logistic regression model for this composite outcome that included these factors and their interaction. To compare the left ventricular ejection fraction (LVEF) before and after percutaneous occlusion, a linear mixed effects model with time point (before the procedure, <24-48 hours after the procedure, and at discharge/latest follow-up), group (VLW vs LW), and their interaction, with a random patient-level intercept, was performed. Linear mixed effects models for the continuous outcome (pulmonary score) and logistic mixed models for the binary outcomes (need for mechanical ventilation, diuretic use) with Dunnett's correction for multiple comparisons. *P* values of <.05 were considered significant.

Results

Among 416 patients referred for percutaneous PDA closure at our institution, 106 lower weight infants met clinical criteria and 14 were procedural failures (**Figure 1**). Reasons for procedural failures are provided in **Table I** (available at www.jpeds.com). Subsequent analyses are based on 92 lower weight infants that left the catheterization laboratory with a device (technical success).

Baseline patient characteristics of the cohort are shown in **Table II**. Fewer than one-half of infants received either prophylactic indomethacin (18/92 [20%]) or medical treatment (24/92 [26%]) with indomethacin or ibuprofen before referral for percutaneous occlusion. Most infants (54/92 [59%]) had a diagnosis of bronchopulmonary dysplasia. The primary reason for referral was respiratory insufficiency with infants receiving either mechanical ventilation (35/92 [38%]) or noninvasive respiratory support with continuous positive airway pressure or nasal cannula (57/92 [62%]) at the time of referral. The majority also had evidence of left ventricular volume loading (68/92 [74%]). At the time of procedure, 32 of the 92 infants (35%) were VLW and 4 infants weighed <2 kg; 90 of the 92 infants (98%) were >28 days of age at the time of catheterization and 76 of the 92 (83%) were >2 months' postnatal age.

Before percutaneous occlusion, PDA shunt flow was left to right (81/92 [88%]) or bidirectional (11/92 [12%]); none were exclusively right to left. Among those with a bidirectional shunt, the mean ± SD proportion of the cardiac cycle with right-to-left shunt was 23% ± 12%. The DA diastolic flow was anterograde throughout diastole (50/92 [54%]), no clear direction to diastolic flow (4/92 [4%]), and retrograde throughout diastole (38/92 [41%]).

Immediate procedural outcomes and complications are shown in **Table III** (available at www.jpeds.com). Femoral arterial and venous access was obtained in all cases. Classification of ductal morphology included type A in 19

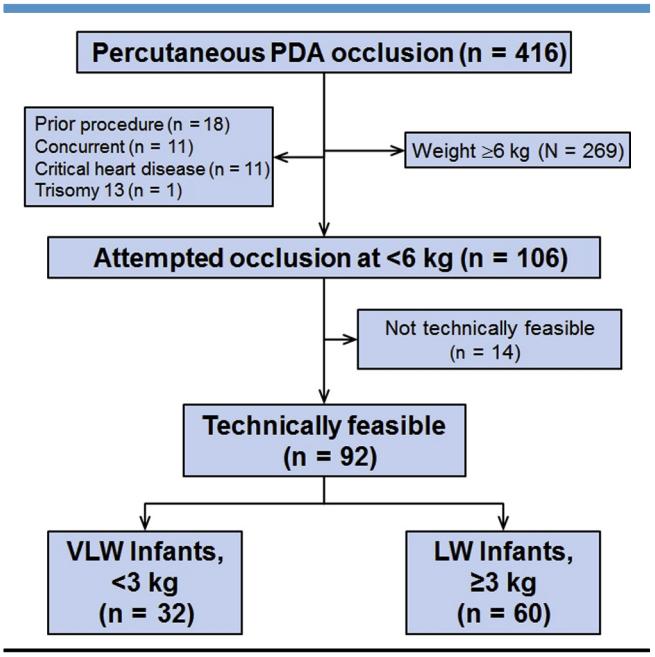

Figure 1. Flowchart of patient selection for inclusion.

(21%), type C in 40 (43%), type E in 15 (16%), and complex (mixed type ducts) in 18 (20%) cases. At the time of PDA closure, 58 infants (63%) had evidence of PH.[18] In 37 cases (40%), the procedure required repositioning with the same device (n = 20) or replacement with a larger device (n = 17). No deaths were observed during the procedure.

Within 24 hours after the procedure 24 of the 92 infants (26%) received treatment for hypotension (**Table IV**). Among infants with oxygenation failure, 3 were started on inhaled nitric oxide. The decreases in LVEFs immediately after the procedure were greater among VLW infants (11.4%) than in LW infants (5.4%; $P < .01$; **Figure 2**; available at www.jpeds.com). Among infants (n = 12/92 [13%]) with evidence of decreased left ventricular systolic, the majority were mild (n = 11); 1 infant weighing 2.6 kg at the time of percutaneous occlusion had a moderate decrease in LVEF (preprocedure value, 64%; immediate postocclusion value, 34%) this infant received epinephrine to augment cardiac performance. The timing of the immediate postprocedure echocardiogram included: 0-<12 hours in 19 (21%), 12-<24 hours in 62 (67%), 24-<36 hours in 4 (4%), 36-<48 hours in 4 (4%), >48 hours in 3 (3%). We observed no differences in the timing (mean ± SD) of the postoperative echocardiogram among infants with postligation cardiac syndrome vs infants without postligation cardiac syndrome (19 ± 4 hours vs 23 hours ± 4; $P = .17$).

Immediately after device placement, LPA obstruction was observed on echocardiogram in 20 infants (22%). Among infants with evidence of LPA obstruction on the initial postprocedural echocardiogram, persistent LPA obstruction at 1 month after closure and discharge was observed among

Table II. Demographics

Characteristics	Infants (n = 92)
Birth weight (g)	1196 (475-4165)
Completed weeks of gestation*	
23-25	20 (22)
26-28	22 (24)
29-31	8 (9)
≥32	38 (41)
Female sex	50 (54)
Additional cardiac defects	46 (50)
Atrial-septal defect	38 (41)
Ventricular septal defect	12 (13)
Atrioventricular septal defect	2 (2)
Genetic/chromosomal anomalies	16 (17)
Age at procedure (months)	3.0 (0.5-11.1)
Weight at procedure (kg)	3.7 (1.4-5.9)

Data are median (range), number (%) or mean ± SD.
*Age at birth unknown (n = 4).

40% (8/20) and 15% (3/20) of infants, respectively (**Figure 3**, A; available at www.jpeds.com). We observed 2 cases of mild LPA obstruction not observed on the initial postprocedure echocardiogram, but observed on a later, subsequent echocardiogram 1 month after closure (late-onset obstruction); in both cases, no evidence of LPA obstruction was observed at discharge.

Immediately after device placement, DA obstruction was observed on echocardiogram in 7 infants (8%), with median maximal instantaneous gradients of 17 mm Hg (range, 16-38 mm Hg). Among infants with evidence of DA obstruction on the initial postprocedural echocardiogram, persistent DA obstruction at 1 month after closure and discharge was observed among 4 infants at both time-points, respectively (**Figure 3**, B). We observed 3 cases of DA obstruction not observed on the initial postprocedure echocardiogram, but observed on echocardiograms 1 month after the procedure ("late-onset obstruction"); in 2 of the 3 cases of late-onset obstruction, no evidence of DA obstruction was observed on the echocardiogram at discharge. Among the cohort, we observed 3 infants with evidence of LPA and DA obstruction. Agreement on evidence LPA or DA device obstruction (yes/no) and severity of obstruction (mild vs moderate) was good, with a κ of 0.93 and 0.85, respectively.

Two infants (2/92 [2%]) met the criteria for procedural failure. Both cases had evidence of persistent hemolysis secondary to the device and underwent surgical ligation of the ductus and device removal. Two infants (2/92 [2%]) had evidence of residual ductal shunting by color flow Doppler on the initial postprocedure echocardiogram, but this shunting was not apparent on subsequent studies. We observed no evidence of late embolization. None of the preprocedural variables of interest were associated with the composite outcome of a device-related complication (**Table V**; available at www.jpeds.com). We observed no differences in adverse cardiopulmonary outcomes among infants with PH vs infants without PH (**Table VI**; available at www.jpeds.com). When a multivariable model that included procedural weight (centered), procedural age (centered), and an interaction between weight and age was fit for the occurrence of a device-related complication, none of the variables predicted the composite outcome.

Table IV. Device-related complications and cardiopulmonary outcomes

Characteristics	Total (n = 92)	<3 kg (n = 32)	≥3 kg (n = 60)	*P* value
Cardiopulmonary outcomes				
Treatment of hypotension	24 (26)	10 (31)	14 (23)	.46
Epinephrine	1 (1)	1 (3)	1 (2)	–
Red blood cell transfusion	22 (24)	10 (31)	13 (22)	.32
Epinephrine and red blood cell transfusion	1 (1)	1 (3)	0 (0)	–
Oxygenation failure	13 (14)	9 (28)	4 (8)	<.01
Decreased left ventricular systolic function*,†	12 (13)	9 (29)	3 (5)	<.01
Postligation cardiac syndrome	7 (8)	4 (13)	3 (6)	.23
Composite adverse cardiopulmonary outcomes†	12 (13)	9 (29)	3 (5)	<.01
Device-related complications				
LPA obstruction‡	22 (24)	8 (25)	14 (23)	>0.99
Mild obstruction	21 (23)	8 (25)	13 (22)	.80
Moderate obstruction	1 (1)	0 (0)	1 (2)	–
DA obstruction§	10 (11)	2 (6)	8 (13)	.48
Residual shunting	2 (2)	1 (3)	1 (2)	>0.99
Late embolization	0 (0)	0 (0)	0 (0)	–
Failed closure	2 (2)	1 (3)	1 (2)	>0.99
Composite device-related complication¶	30 (33)	10 (31)	20 (33)	>0.99

LPA, left pulmonary artery.
Data shown as number (% of column), except where otherwise indicated.
Severity of LPA obstruction was based on the following peak instantaneous Doppler velocity obtained by echocardiogram: mild (≥2.0 to <3.0 m/s), moderate (≥3.0 m/s).
*All infants with decreased left ventricular systolic function were mildly reduced (EF of 41%–55%).
†Denominators adjusted for missing data.
‡Includes 2 cases of late-onset obstruction of LPA not observed on the initial postprocedure echocardiogram.
§Includes 3 cases of late-onset obstruction of DA not observed on the initial postprocedure echocardiogram.
¶Some infants had multiple device-related complications.

Compared with preprocedure values, the pulmonary score decreased over time following PDA closure (**Figure 4**, **A**; linear mixed effects model, $P < .01$). Compared with preprocedure baselines, the likelihood to receive mechanical ventilation (**Figure 4**, **B**; logistic mixed effects model, $P < .01$), and the use of diuretics (**Figure 4**, **C**; logistic mixed effects model, $P < .01$), decreased after PDA closure.

Outpatient data were available in 81 infants (88%) with a median follow-up time of 3 years (range, 1-8 years). Among 3 cases with persistent mild LPA obstruction at discharge, 2 had ventilation/perfusion scans at 10 and 37 months after the procedure. One scan showed asymmetry normal flow split (57% to the right lung and 43% to left lung), the other showed asymmetric split lung perfusion (77% to the right lung and 23% to the left lung). No infants have undergone reintervention to address LPA obstruction. Among 5 cases with evidence of DA obstruction at discharge, none have had symptomatology attributed to the obstruction, with a median upper extremity/lower extremity gradient of <15 mm Hg in all patients. None have undergone reintervention to address the DA obstruction.

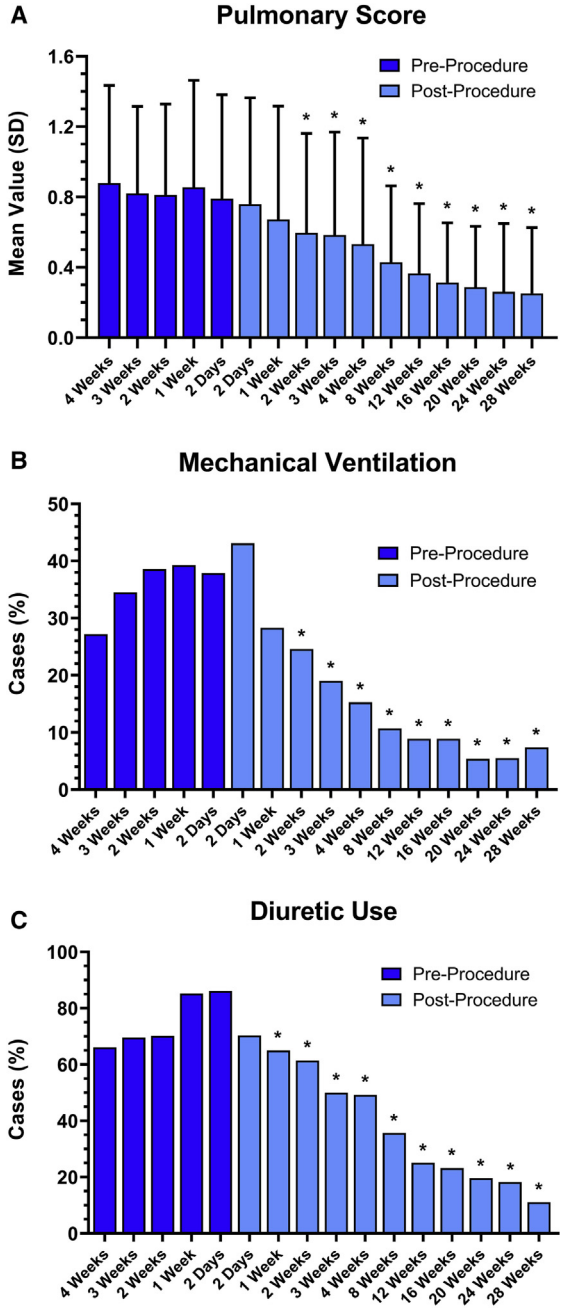

Figure 4. The *x*-axis represents time before and after the procedure. The *y*-axis designates percentage of cases with outcomes of interest. Post-procedural outcomes were compared to pre-procedure baseline, designated at 2 days before the procedure, with Dunnett's correction for multiple comparisons. **A,** Compared to pre-procedural baseline, the pulmonary scores following PDA closure decreased (linear mixed effects model, *Adjusted $P < .01$). **B,** Compared with preprocedure baseline, the proportion of infants on mechanical ventilation after PDA closure decreased (logistic mixed effects model, *Adjusted $P < .01$). **C,** Compared with preprocedure baseline, the proportion of infants receiving diuretics following PDA closure decreased (logistic mixed effects model, *Adjusted $P < .01$). Diuretics included furosemide, bumetanide, chlorothiazide, hydrochlorothiazide, and spironolactone.

Among 56 infants with evidence of PH before the procedure, 12 (21%) had evidence of PH at discharge and were followed in the outpatient cardiology clinic. Among these infants, after normalization of PH on echocardiogram, 11 have been weaned off anti-PH medications at last known follow-up (median, 3 years; range, 1-12 years); 1 infant remains on sildenafil at 52 months' postnatal age.[18] We observed 4 deaths after the initial hospital discharge, none of which were attributed to the percutaneous occlusion: presumed sepsis (n = 2), liver dysfunction with associated coagulopathy owing to macrophage activation syndrome (n = 1), and respiratory arrest (n = 1).

Discussion

The main finding of our study is that percutaneous PDA occlusion in lower weight infants may offer longer term respiratory benefits,[23] but also have risks of adverse cardiopulmonary outcomes and device-related complications. Although the present study provides insights into the risk/benefit profile of percutaneous PDA occlusion in lower weight infants, the absence of a direct comparison group of infants with similar PDA dynamics and risk factors who did not undergo percutaneous PDA closure limit the interpretability of the current findings.

Consistent with previous studies, 10%-15% of lower weight infants referred for percutaneous PDA closure were not closed in the catheterization suite and were referred for surgical ligation.[2] Although not used in the present study, novel devices that address differences in ductal morphology among lower weight infants compared with more mature counterparts are now available.[23] The US Food and Drug Administration recently approved the Amplatzer Piccolo Occluder; a device manufactured with the purpose of closing the PDA among infants with weights of >700 g.[24] These modifications, as well as refinements in procedural techniques and increasing operator experience, are likely to change risk/benefit profiles over time.[15,25-27]

Similar to surgical PDA ligation, age and weight at the time of procedure may be a risk factor for cardiopulmonary compromise after percutaneous occlusion.[18,28] Irrespective of the method of ductal closure (percutaneous, surgery), immaturity of the myocardium and underdeveloped adaptive mechanisms to overcome the increase in LV afterload, particularly in VLW infants, may contribute to decreased cardiac performance after device placement.[29,30] Although rates of postligation cardiac syndrome in our cohort were lower than those reported among infants undergoing surgical ligation (31%-35%), those comparisons can be misleading.[12,13] Teixeira et al showed that rates of adverse cardiopulmonary outcomes after surgical ligation markedly decrease beyond 28 postnatal days.[12] Because 98% of infants in our cohort were >28 days of age at the time of percutaneous PDA occlusion, lower rates of postligation cardiac syndrome are not surprising. Additionally, although the risks of adverse cardiopulmonary outcomes are usually present in the first hours

(<12 hours) after ductal closure,[30,31] most infants in our cohort had an echocardiogram 12-24 hours after the procedure. In the absence of direct comparison among lower weight infants warranting PDA closure, the central question of whether surgery or percutaneous occlusion is the preferred treatment remains unanswered.[2] Previous reports of an association between surgical PDA ligation and adverse neonatal outcomes failed to adjust for a number of confounders (survival bias, residual bias owing to confounding by indication).[29,32] Thus, surgery remains a reasonable option for a subgroup of higher risk infants requiring ductal closure.

We offer a number of explanations for higher rates of device-related obstruction than those reported previously.[25] The lack of standardized definitions for device-related obstruction is acknowledged,[11] wherein we included even mild (>2 m/s) cases of LPA obstruction. Interestingly, our rate of LPA obstruction at longest follow-up (3%) is consistent with previous investigators.[15] The timing and nature of surveillance after device closure are not reported consistently in the literature.[15,16] Although postclosure surveillance in our cohort was comprehensive, including independent review of a large number of echocardiograms, there are known limitations of echocardiography in the accurate assessment of device-related obstruction.[16] Although our observation of late-onset obstruction among a subgroup of infants may reflect changes over time in device positioning, a more likely explanation is that the obstruction was present, but not detected, on the initial echocardiogram after device closure. Because lung disease and mechanical ventilation limit acoustic windows, more robust surveillance tools (ventilation/perfusion scans) may be useful.[16] Similar to previous studies,[14,16] a number of patients that went on to receive surgery (failed percutaneous occlusion) had preexisting stenosis (preclosure gradients) in the LPA and DA; this is an important consideration in evaluating the feasibility and risk/benefit profile of the procedure.

This study has several limitations. We acknowledge the risk of referral bias, because the study was conducted at a large, pediatric academic center. Baseline characteristics (bronchopulmonary dysplasia, genetic/chromosomal abnormalities), exposure to ductal shunting (flow and pressure related vascular remodeling), and indications for percutaneous occlusion (respiratory insufficiency) may explain the observed rates of PH. Because this was a retrospective study of eligible patients treated at a single institution, no a priori power and sample size calculations were performed. The primary reason and timing of referral for PDA closure varied markedly. Despite well-defined inclusion and exclusion criteria, one-half of the infants in the present study had additional cardiac defects. Similar to previous studies, we chose LVEF as a pragmatic cardiac marker of cardiac performance[25]; however, LVEF represents only a single echocardiographic measure with limitations (preload and afterload dependent, moderate reproducibility). Thresholds to provide treatment for hypotension were not standardized. Although mechanisms remain unknown, growth and remodeling of the vasculature may have contributed to the decreases we observed in device-related obstruction over time.[33] We made efforts to adjudicate outcomes independently, but complications may be tied to a number of patient-specific variables. Observed improvements in longer term respiratory status after percutaneous occlusion cannot be solely attributed to the procedure and may be the consequence of unknown factors (eg, nutrition, linear growth).

Percutaneous ductal closure may offer respiratory benefits in high-risk infants, but rates of adverse cardiopulmonary outcomes in the immediate postprocedural period and device-related complications underscore the need for continued device modifications for lower weight infants. Once the optimal device for percutaneous PDA occlusion in this subgroup of infants is identified, comparative studies between percutaneous PDA occlusion vs alternative treatment strategies will be necessary to guide the practice of evidence-based medicine. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Schneider DL, Moore JW. Patent ductus arteriosus. Circulation 2006;114:1873-82.
2. Backes CH, Kennedy KF, Locke M, Cua CL, Ball MK, Fick TA, et al. Transcatheter occlusion of the patent ductus arteriosus in 747 infants <6 kg: insights from the NCDR IMPACT Registry. JACC Cardiovasc Interv 2017;10:1729-37.
3. Lam JY, Lopushinsky SR, Ma IWY, Dicke F, Brindle ME. Treatment options for pediatric patent ductus arteriosus: systematic review and meta-analysis. Chest 2015;148:784-93.
4. Prieto LR, DeCamillo DM, Konrad DJ, Scalet-Longworth L, Latson LA. Comparison of cost and clinical outcome between transcatheter coil occlusion and surgical closure of isolated patent ductus arteriosus. Pediatrics 1998;101:1020-4.
5. Moore JW, Greene J, Palomares S, Javois A, Owada CY, Cheatham JP, et al. Results of the combined U.S. Multicenter Pivotal Study and the Continuing Access Study of the Nit-Occlud PDA device for percutaneous closure of patent ductus arteriosus. JACC Cardiovasc Interv 2014;7:1430-6.
6. AGA Medical Corporation. Amplatzer duct occluder II: instructions for use. Plymouth, MN: AGA Medical Corporation; 2013.
7. Backes CH, Cheatham SL, Deyo GM, Leopold S, Ball MK, Smith CV, et al. Percutaneous patent ductus arteriosus (PDA) closure in very preterm infants: feasibility and complications. J Am Heart Assoc 2016;5:e002923.
8. Costello JM, Polito A, Brown DW, McElrath TF, Graham DA, Thiagarajan RR, et al. Birth before 39 weeks' gestation is associated with worse outcomes in neonates with heart disease. Pediatrics 2010;126:277-84.
9. Boghossian NS, Hansen NI, Bell EF, Stoll BJ, Murray JC, Carey JC, et al. Mortality and morbidity of VLBW infants with trisomy 13 or trisomy 18. Pediatrics 2014;133:226-35.
10. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723-9.

11. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA , Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. J Am Soc Echocardiogr 2002;15:167-84.
12. Teixeira LS, Shivananda SP, Stephens D, Van Arsdell G, McNamara PJ. Postoperative cardiorespiratory instability following ligation of the preterm ductus arteriosus is related to early need for intervention. J Perinatol 2008;28:803-10.
13. Ulrich TJB, Hansen TP, Reid KJ, Bingler MA, Olsen SL. Post-ligation cardiac syndrome is associated with increased morbidity in preterm infants. J Perinatol 2018;38:537-42.
14. Gowda ST, Kutty S, Ebeid M, Qureshi AM, Worley S, Latson LA. Preclosure pressure gradients predict patent ductus arteriosus patients at risk for later left pulmonary artery stenosis. Pediatr Cardiol 2009;30:883-7.
15. VanLoozen D, Sandoval JP, Delaney JW, Pedra C, Calamita P, Dalvi B, et al. Use of Amplatzer vascular plugs and Amplatzer duct occluder II additional sizes for occlusion of patent ductus arteriosus: a multi-institutional study. Catheter Cardiovasc Interv 2018;92:1323-8.
16. Kharouf R, Heitschmidt M, Hijazi ZM. Pulmonary perfusion scans following transcatheter patent ductus arteriosus closure using the Amplatzer devices. Catheter Cardiovasc Interv 2011;77:664-70.
17. Saida K, Nakamura T, Hiroma T, Takigiku K, Yasukochi S. Preoperative left ventricular internal dimension in end-diastole as earlier identification of early patent ductus arteriosus operation and postoperative intensive care in very low birth weight infants. Early Hum Dev 2013;89:821-3.
18. Mourani PM, Sontag MK, Younoszai A, Ivy DD, Abman SH. Clinical utility of echocardiography for the diagnosis and management of pulmonary vascular disease in young children with chronic lung disease. Pediatrics 2008;121:317-25.
19. Bergersen L, Gauvreau K, Marshall A, Kreutzer J, Beekman R, Hirsch R, et al. Procedure-type risk categories for pediatric and congenital cardiac catheterization. Circ Cardiovasc Interv 2011;4:188-94.
20. El-Said HG, Bratincsak A, Foerster SR, Murphy JJ, Vincent J, Holzer R, et al. Safety of percutaneous patent ductus arteriosus closure: an unselected multicenter population experience. J Am Heart Assoc 2013;2:e000424.
21. Krichenko A, Benson LN, Burrows P, Moes CA, McLaughlin P, Freedom RM. Angiographic classification of the isolated, persistently patent ductus arteriosus and implications for percutaneous catheter occlusion. Am J Cardiol 1989;63:877-80.
22. Madan A, Brozanski BS, Cole CH, Oden NL, Cohen G, Phelps DL. A pulmonary score for assessing the severity of neonatal chronic lung disease. Pediatrics 2005;115:e450-7.
23. Sathanandam S, Balduf K, Chilakala S, Washington K, Allen K, Knott-Craig C, et al. Role of transcatheter patent ductus arteriosus closure in extremely low birth weight infants. Catheter Cardiovasc Interv 2019;93:89-96.
24. United States National Institutes of Health, US National Library of Medicine. AMPLATZER Duct Occluder II Clinical Study (ADO II). https://clinicaltrials.gov/ct2/show/NCT00713700?term=ADO+II&rank=2. Accessed February 1, 2019.
25. Zahn EM, Peck D, Phillips A, Nevin P, Basaker K, Simmons C, et al. Transcatheter closure of patent ductus arteriosus in extremely premature newborns: early results and midterm follow-up. JACC Cardiovasc Interv 2016;9:2429-37.
26. Gruenstein DH, Ebeid M, Radtke W, Moore P, Holzer R, Justino H. Transcatheter closure of patent ductus arteriosus using the AMPLATZER duct occluder II (ADO II). Catheter Cardiovasc Interv 2017;89:1118-28.
27. Zahn EM, Nevin P, Simmons C, Garg R. A novel technique for transcatheter patent ductus arteriosus closure in extremely preterm infants using commercially available technology. Catheter Cardiovasc Interv 2015;85:240-8.
28. McNamara PJ, Stewart L, Shivananda SP, Stephens D, Sehgal A. Patent ductus arteriosus ligation is associated with impaired left ventricular systolic performance in premature infants weighing less than 1000 g. J Thorac Cardiovasc Surg 2010;140:150-7.
29. Weisz DE, Giesinger RE. Surgical management of a patent ductus arteriosus: is this still an option? Semin Fetal Neonatal Med 2018;23:255-66.
30. Noori S, Friedlich P, Seri I, Wong P. Changes in myocardial function and hemodynamics after ligation of the ductus arteriosus in preterm infants. J Pediatr 2007;150:597-602.
31. Jain A, Sahni M, El-Khuffash A, Khadawardi E, Sehgal A, McNamara PJ. Use of targeted neonatal echocardiography to prevent postoperative cardiorespiratory instability after patent ductus arteriosus ligation. J Pediatr 2012;160:584-9.e1.
32. Weisz DE, Mirea L, Resende MHF, Ly L, Church PT, Kelly E, et al. Outcomes of surgical ligation after unsuccessful pharmacotherapy for patent ductus arteriosus in neonates born extremely preterm. J Pediatr 2018;195:292-6.e3.
33. Du ZD, Roguin N, Barak M, Hershkowitz S, Milgram E, Brezins M. Doppler echocardiographic study of the pulmonary artery and its branches in 114 normal neonates. Pediatr Cardiol 1997;18:38-42.

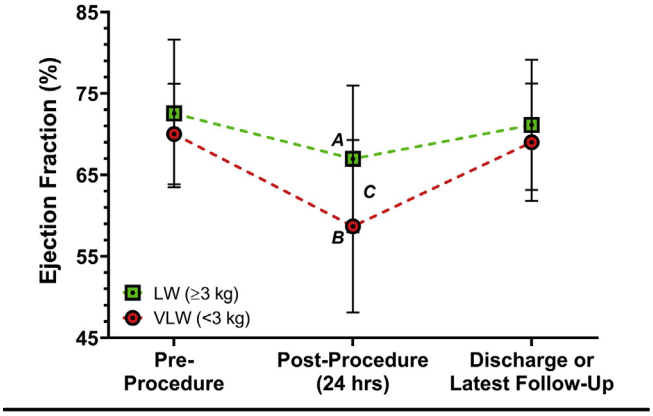

Figure 2. **A,** Among VLW infants, compared with preprocedure values (70.0%), the LVEF decreased immediately after the procedure (VLW infants, 58.5% [$P < .01$]; LW infants), but returned to baseline values at discharge or longest follow-up (69.1%; $P = .58$). **B,** Among LW infants, compared with preprocedure values (72.5%), the LVEF decreased immediately after the procedure (67.1%; $P < .01$), but returned to baseline values at discharge or longest follow-up (70.9%; $P = .24$). **C,** Compared with preprocedure values, the decrease in LVEF immediately after the procedure was greater among VLW infants (11.4%) than LW infants (5.4%; $P < .01$).

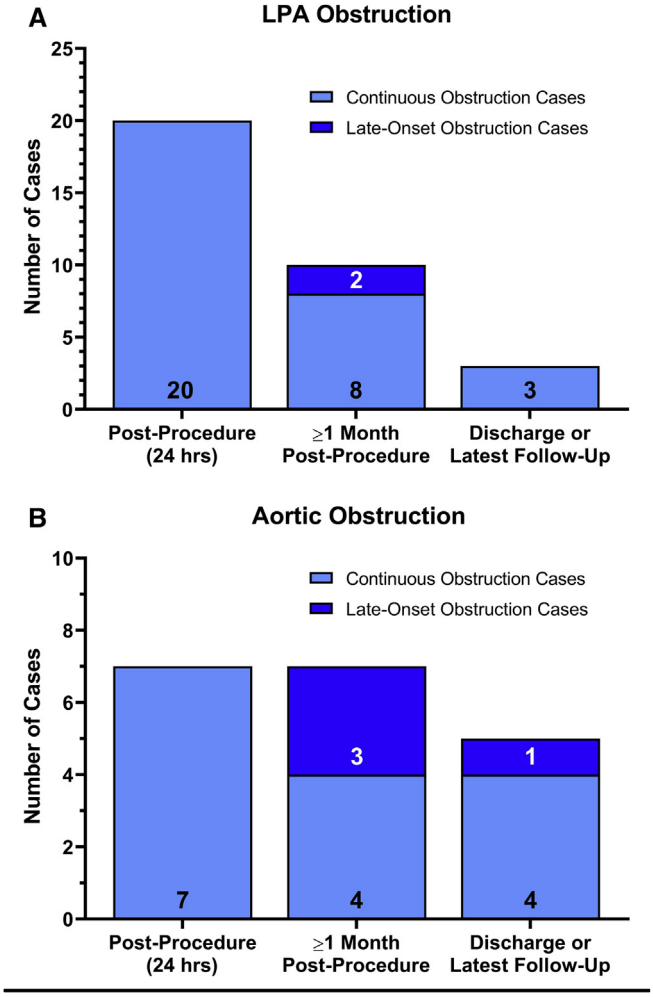

Figure 3. **A,** Incidence of LPA obstruction observed over time. **B,** Incidence of DA obstruction observed over time. Late-onset obstruction was defined as evidence of LPA or DA obstruction not observed on the initial postprocedure echocardiogram, but observed on subsequent imaging. The number of infants evaluated across the time points include preprocedure (n = 92), ≥1 month after the procedure (n = 90), and at discharge or latest follow-up (n = 89).

Table I. Failed percutaneous PDA closure cases

Cases	Description of events or issues	Age (mo)	Patient weight (kg)	PDA classification	Type of device(s), if applicable	Outcome
1	Complications requiring CPR	1.0	3.8	C	*	Surgical ligation
2	Hypoplasia of the aortic isthmus	6.0	5.1	C/D	†	Surgical ligation
3	Not amenable to percutaneous occlusion‡	3.0	5.0	A	†	Surgical ligation
4	Not amenable to percutaneous occlusion‡	3.0	2.3	C	6 mm AVP-II	Surgical ligation
5	Not amenable to percutaneous occlusion§	1.0	3.1	C	†	Surgical ligation
6	Embolization requiring surgical retrieval	3.0	2.2	C	4 mm AVP-II	Surgical ligation
7	Not amenable to percutaneous occlusion§	2.0	2.7	C	6 mm AVP-II	Surgical ligation
8	Not amenable to percutaneous occlusion§	0.5	4.0	A	5/4 ADO	Surgical ligation
9	Embolization requiring retrieval	1.0	3.0	C	6 mm AVP-II	Spontaneous closure¶
10	Not amenable to percutaneous occlusion§	2.0	5.9	B	†	Surgical ligation
11	Not amenable to percutaneous occlusion§	3.0	2.6	C	10 mm AVP-II	Surgical ligation
12	Embolization requiring surgical retrieval	4.0	4.5	C	10 mm AVP-II	Surgical ligation
13	Not amenable to percutaneous occlusion**	1.0	2.6	B	5/4 ADO	Surgical ligation
14	Not amenable to percutaneous occlusion‡	3.0	3.2	B	5/4 ADO	Surgical ligation

ADO, Amplatzer Ductal Occluder; *AVP-II*, Amplatzer Vascular Plug; *CPR*, cardiopulmonary resuscitation (eg, chest compressions); *LPA*, left pulmonary artery.
*Attempt at device closure aborted owing to acute cardiopulmonary decompensation in the catheterization laboratory requiring CPR.
†Infant taken to catheterization laboratory for attempted percutaneous occlusion, but angiography concerning for preexisting DA or LPA obstruction before device placement.
‡Placement of device resulted in LPA gradient that prevented safe release of device.
§Placement of device resulted in DA gradient that prevented safe release of device.
¶Echocardiogram revealed ductus closed spontaneously after the attempted percutaneous occlusion.
**Placement of device resulted in DA gradient and LPA gradient that prevented safe release of device.

Table III. Immediate procedural data and adverse events

Characteristics	Infants (n = 92)
Procedural data	
Radiation dose (mGy)*	83.5 (16.0-880.0)
Contrast dose (mL/kg)*	5.0 (2.1-11.1)
General anesthesia	92 (100)
Minimal PDA length (mm)	10.1 (4.3-22.0)
Minimal PDA diameter at the aortic ampulla (mm)	5.2 (1.3-11.3)
Minimal PDA diameter at the pulmonary artery (mm)	3.1 (1.0-7.4)
Arterial catheter size	
2.5F	1 (1)
3.0F	22 (24)
3.3F	36 (39)
4.0F	33 (37)
Venous catheter size	
4F	13 (14)
5F	52 (57)
6F	25 (27)
7F	3 (3)
Devices used for PDA closure	
ADO	26 (28)
AVP I	4 (4)
AVP-II	61 (66)
Flipper coil	1 (1)
Adverse events	
Severity level 1 (equipment failure or malfunction)	1 (1)
Severity level 2	12 (13)
Arrhythmia, self-correcting	6 (7)
Loss of pulse or limb noted to be dusky (treatment not required)	4 (4)
Excessive blood loss (red blood cell transfusion not required)	1 (1)
Hematoma noted at access site	1 (1)
Severity level 3	25 (27)
Required red blood cell transfusion in catheterization lab	18 (20)
Arrhythmia requiring intervention (medical)	1 (1)
Loss of pulse in limb requiring intervention (heparin)	4 (4)
Embolization/malposition requiring retrieval of device after release	2 (2)
Severity level 4	5 (5)
Hypotension requiring inotropic support	2 (2)
Atrioventricular block requiring intervention	1 (1)
Respiratory compromise owing to unanticipated extubation	2 (2)
Severity level 5 (death or need for ECMO)	0 (0)

ADO, Amplatzer Ductal Occluder; *AVP*, Amplatzer Vascular Plug; *ECMO*, extracorporeal membrane oxygenation.
Data are shown as median (range) and number (% of cohort).
*Data not available (n = 11).

Table V. Associations between patient, procedural and device-related characteristics and any device-related complication

Variables	No device-related complications (n = 62)	Device-related complication (n = 30)	*P* value
Procedural weight	3.7 ± 1.1	3.7 ± 1.2	.97
Procedural age (months)	3.5 ± 2.0	3.1 ± 1.5	.47
Type C PDA	25 (40)	15 (50)	.50
Genetic/chromosomal anomaly	13 (21)	3 (10)	.25
Evidence of PH*	39 (63)	17 (57)	.65
AVP-II device	39 (63)	22 (73)	.36

AVP-II, Amplatzer Vascular Plug-II.
Values shown are number (%) or mean ± SD.
*As determined by hemodynamic catheterization during procedure.

Table VI. Comparison of adverse cardiopulmonary outcomes among infants with PH vs infants without PH

Outcomes	Pulmonary hypertension (n = 56)	No pulmonary hypertension (n = 36)	*P* value
Treatment of hypotension	14 (25)	10 (28)	.96
Oxygenation failure	9 (16)	4 (11)	.56
Decreased left ventricular systolic function*	7 (13)	5 (14)	>0.99
Postligation cardiac syndrome	5 (9)	2 (6)	>0.99
Composite adverse cardiopulmonary outcomes*	7 (13)	5 (14)	>0.99

Data shown as number (% of column), except where otherwise indicated.
*Denominator adjusted for missing data.