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Patent ductus arteriosus and the risk of bronchopulmonary dysplasia-associated pulmonary hypertension

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Abstract

Background: To determine whether prolonged exposure to a moderate/large patent ductus arteriosus left-to-right shunt (PDA) increases the risk of late (beyond 36 weeks) pulmonary hypertension (BPD-PH) and pulmonary vascular disease (BPD-PVD) during the neonatal hospitalization in preterm infants (<28 weeks' gestation) with bronchopulmonary dysplasia (BPD).

Methods: All infants requiring respiratory support ≥36 weeks had systematic echocardiographic evaluations for BPD-PH at planned intervals. Infants were classified as having either flow-associated BPD-PH (BPD-flow-PH) or BPD-PVD.

Results: 256 infants survived ≥36 weeks: 105 had NO BPD (were off respiratory support by 36 weeks); 151 had BPD. 22/151 had BPD-PH (12/22 had BPD-flow-PH from a PDA that persisted beyond 36 weeks; 10/22 had BPD-PVD). Moderate/large PDA shunts that persisted beyond 36 weeks were significantly associated with an increased incidence of BPD-PH due to BPD-flow-PH. We found no association between the duration of PDA exposure and the incidence of BPD-PVD.

Conclusion: Moderate/large PDA shunts increase the risk of flow-associated BPD-PH when present beyond 36 weeks. Although term infants with PDA-congenital heart disease can

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1) Hythem Nawaytou, Nancy K. Hills, and Ronald I. Clyman made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data.

2) Hythem Nawaytou, Nancy K. Hills, and Ronald I. Clyman have drafted the article or revised it critically for important intellectual content.

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develop pulmonary vascular remodeling and PVD after months of PDA exposure, we found no echocardiographic evidence in preterm infants that prolonged PDA exposure increases the incidence of BPD-PVD during the neonatal hospitalization.

Introduction:

Preterm infants delivered at <28 weeks' gestation have a high incidence of bronchopulmonary dysplasia (BPD), defined by the amount of respiratory support they need beyond 36 weeks' post menstrual age (PMA) [1-4]. In addition to the alterations in respiratory compliance and airway resistance that accompany BPD, a subset of infants will develop pulmonary artery hypertension (PH) as a comorbidity that persists beyond 36 weeks. Infants with BPD-associated pulmonary hypertension (BPD-PH) have a substantially increased risk of morbidity and mortality [5, 6].

The factors responsible for the elevated pulmonary vascular pressures in infants with BPD-PH are usually unknown. Since pulmonary blood pressure is related to blood flow and vascular resistance through the equation *Pressure = Flow x Resistance,* most cases of BPD-PH can be grouped into two broad categories: 1) increased pulmonary blood flow (Flow-associated PH) (e.g., left-to-right flow through shunts like the patent ductus arteriosus (PDA) or ventricular septal defect (VSD)), and 2) increased pulmonary vascular resistance or obstruction (e.g., pulmonary vascular diseases/disorders (PVD) like altered vasoreactivity, vascular injury, remodeling, maldevelopment, or pulmonary venous obstruction).

Distinguishing between the two broad categories is important since flow-associated PH can usually be eliminated when the shunt is closed, whereas PVD and abnormal vascular growth appear to be more persistent and may contribute to impaired alveolar development and parenchymal lung disease. Although the development of PVD was initially attributed to the severity of an infant's lung disease [7], there is increasing evidence to suggest that additional risk factors, including those that predate birth, contribute to the development of BPD-associated PVD [8-10].

Several risk factors for BPD-PH have been consistently identified in observational studies and their meta-analyses [11-13]. BPD-PH is most frequently seen in infants with the most severe grades of BPD and those who are small for gestational age (SGA). Other consistently observed postnatal risk factors include the duration of invasive ventilation, severe retinopathy of prematurity (sROP), and the presence of a persistent PDA [13].

We were particularly interested in examining how prolonged exposure to a persistent PDA might be associated with the development of BPD-PH in preterm infants. A moderate/large PDA L-R shunt can produce both flow-associated PH and PVD. The initial increased L-R flow through the PDA shunt causes an acute hydraulic increase in pulmonary blood pressure [14, 15]. In addition, direct transmission of systemic blood pressures through the shunt to the pulmonary circulation adds to the flow associated PH. Over time prolonged exposure of the pulmonary circulation to the shunt's high pressures and flow will cause pulmonary vascular remodeling and the development of PVD of varying severity. In term infants with PDA-congenital heart disease months of prolonged PDA exposure can cause irreversible

PVD and right-to-left ductal shunting (with Eisenmenger physiology being the most extreme end of the spectrum) [16, 17].

We hypothesized that extremely preterm infants might be particularly vulnerable to the effects of a persistent left-to-right PDA shunt on pulmonary vascular remodeling. We designed the following observational study to examine the relationship between different durations of exposure to moderate/large, left-to-right PDA shunts and the outcomes BPD-PH, flow-associated PH, and BPD-associated PVD (BPD-PVD) beyond 36 weeks' PMA. We hypothesized that increasing durations of exposure to a moderate/large PDA shunt would accelerate the rate of PVD development and increase the rate of BPD-PVD beyond 36 weeks' PMA in infants born before 28 weeks' gestation.

Methods:

Patient Population:

The study was approved by the Institutional Review Board of the University of California San Francisco. The requirement for individual Research HIPAA Authorization was waived by the Institutional Review Board. Infants were included in the study population if they delivered before $28^{0/7}$ weeks' gestation, were admitted to the intensive care nursery within 24 hours of birth between January 2012 and September 2022 and survived beyond 36 weeks' PMA. A single neonatologist (RIC) recorded all the demographic factors and outcome measures prospectively and reviewed the PDA-focused echocardiograms with the attending cardiologists. A single echo-cardiologist (HN) reviewed the PH focused echocardiograms. Detailed descriptions of our approach to respiratory and hemodynamic support have been previously published [18].

Evaluation and treatment of moderate/large left-to-right PDA shunts:

All infants had an echocardiogram performed on postnatal day 7. The echocardiographic studies included two-dimensional imaging, M-mode, color flow mapping, and Doppler interrogation as previously described [19, 20]. A moderate/large PDA with left-to-right shunt (*PDA L-R shunt*) was defined by continuous left-to-right flow across the PDA, a ductus diameter ≥1.5mm (or PDA:left pulmonary artery diameter ratio ≥0.5), plus one or more of the following criteria: a) left atrium-to-aortic root ratio ≥1.5; b) ductus flow velocity ≤2.5m/sec or mean pressure gradient across the ductus ≤8 mm Hg,; and/or c) reversed diastolic flow in the descending aorta [19, 20]. Ductus that did not meet these criteria were considered "constricted" (small or closed).

Infants who had a moderate/large PDA on the echocardiogram performed on day 7 were followed with echocardiograms every 7 days for the next 2-3 weeks, then at least every 2-3 weeks until the PDA was no longer moderate/large. Infants with a "constricted" (small or closed) ductus on day 7 were examined daily for a change in clinical symptoms indicative of a reopened moderate/large PDA (systolic murmur or hyperdynamic precordium). If either of these occurred, an echocardiogram was performed within 24 hours. When a reopened moderate/large PDA was detected, echocardiograms were performed every 7-10 days for the next 2-3 weeks, and then at least every 2-3 weeks until the PDA was no longer

moderate/large. Infants with a "constricted" ductus that never developed clinical signs of reopening had routine echocardiograms performed at least every 3-4 weeks to confirm ductus constriction until ductus closure or hospital discharge. Infants whose PDAs had not closed before hospital discharge were followed at 2-to-6 months intervals until ductus closure occurred either spontaneously or by device closure.

The duration of exposure to a moderate/large PDA L-R shunt that persisted beyond the first week was calculated and expressed in days. Infants with small or closed ductus at postnatal day 7 were assumed to have been unexposed to a moderate/large PDA L-R shunt during the first 7 days. Infants with moderate/large PDA L-R shunts at postnatal day 7 were assumed to have been exposed to a moderate/large PDA L-R shunt for the entire 7 days. The time of ductus constriction was assigned as the halfway point between the last exam with a moderate/large PDA L-R shunt and the first exam with a constricted ductus. If infants died before an exam showed ductus constriction, the ductus was assumed to be moderate/large at the time of death. When late reopening of the PDA occurred after documented ductus constriction, the additional exposure to the reopened moderate/large PDA L-R shunt (calculated as the number of days from the echocardiogram demonstrating the reopened moderate/large shunt to the time of ductus constriction (i.e., the halfway point between the last exam with a moderate/large PDA L-R shunt and the first exam with a constricted ductus)) was added to the duration of any prior moderate/large PDA L-R shunt exposure.

During the study period, two different protocols for PDA treatment were used. During epoch 1, January 2012 - June 2017, no PDAs were treated during the first 7 days to allow for spontaneous PDA closure [21]. During epoch 2, July 2017 - September 2022, a targeted prophylactic indomethacin treatment approach was used: all infants <25 weeks' gestation as well as infants ≥25 weeks' gestation who still were intubated beyond 24 hours were given prophylactic indomethacin during the first 72 hours. In both epochs, infants with moderate/large PDA L-R shunts could receive pharmacologic treatment with indomethacin or acetaminophen after 8 days if they met prespecified "Rescue" criteria previously described by Clyman et al. [22]. Sixty-nine percent of infants with moderate/large PDA-L-R shunts received pharmacologic PDA treatment. Infants with moderate/large PDA L-R shunts that failed to close after pharmacologic treatment were ligated or had a percutaneous device closure *only if* the infants' ventilatory support was escalating for more than a week or failed to improve after 36 weeks' PMA. PDAs that did not meet the definition of moderate/large PDA L-R shunt were considered to be "*constricted"* (small or closed) and were never treated.

During the no-prophylactic indomethacin epoch, 56% of the infants received pharmacologic treatment (either indomethacin-alone (24%) or acetaminophen with indomethacin back-up (32%)) for a moderate/large PDA L-R shunt after the first week. During the targeted prophylactic indomethacin epoch, 50% of the infants received either prophylactic indomethacin (35%) or pharmacologic treatment (15%) of a moderate/large PDA L-R shunt.

Evaluation of echocardiograms for evidence of PH and PVD:

All infants requiring respiratory support ≥36 weeks' PMA had systematic regular screening echocardiographic assessments for PH as part of the nursery's standards of care protocol

[23, 24]. Beginning at 36 weeks' PMA infants received monthly echocardiograms as long as they were still hospitalized and continued to need some form of respiratory support; after hospital discharge, less frequent echocardiographic examinations (every 2-3 months) were performed until they no longer were receiving respiratory support. If PH-targeted therapy was being considered, infants underwent cardiac catheterization before starting therapy to confirm the diagnosis, assess disease severity, and exclude any other potentially treatable diagnoses [23-26]. Infants who had stopped needing any respiratory support before 36 weeks' PMA were assumed to have little chance of developing PH [23, 24], and therefore did not receive routine screening echocardiograms for PH.

Our echocardiographic criteria for determining PH and PVD have been previously published [27]. An echocardiogram was considered positive for PH if the tricuspid regurgitant jet velocity was >2.9 m/sec, the PDA systolic flow velocity estimated a peak systolic pulmonary artery pressure >35 mm Hg, or if systolic septal flattening was present (based on end-systolic eccentricity index >1.0). The PH was considered to be flow-associated PH, due to the presence of a left-to-right PDA shunt (in the absence of a VSD), if there was left-to-right flow through the PDA in both systole and diastole and the echocardiographic signs of PH disappeared following ductus closure.

An echocardiogram was classified as positive for PVD if it met the above criteria for PH in the absence of a PDA or VSD shunts [27]. If a PDA or VSD shunt was present, the echocardiogram was only classified as positive for PVD if it met the above criteria for PH and there was bidirectional or right-to-left flow through the PDA or VSD, or left-to-right flow through a moderate/large PDA without holodiastolic flow reversal in the abdominal aorta.

Outcomes:

Our goal was to examine the relationship between different durations of moderate/large PDA L-R shunts and the outcomes BPD-PH and BPD-PVD (defined as the incidence of PVD after 36 weeks in infants who also continued to require respiratory support beyond 36 weeks). Our primary outcome was BPD-PVD. Infants who were breathing room air spontaneously and no longer needed respiratory support before they reached 36 weeks were assumed to have no risk of PH and were not evaluated for PH (see above).

We used several different definitions of BPD (*BPD-RS, BPD grades 1-3,* and *BPD 2,3*) to examine the association between the duration of PDA L-R shunt exposure and the outcomes BPD-PH and BPD-PVD after 36 weeks' PMA. *BPD-RS* was defined as needing respiratory support (cannula, nasal positive pressure, or invasive ventilation) beyond 36 weeks' PMA; *BPD grades 1-3,* was defined as needing respiratory support on the day an infant turned $36^{0/7}$ weeks as described by Jensen et al. [4]; and, *BPD grades 2,3,* was defined as needing either nasal cannula flow rates >2 L/min, nasal positive pressure, or invasive mechanical ventilation on the day an infant turned $36^{0/7}$ weeks as described by Jensen et al. [4]. In addition, all infants (except those who required CPAP with ≥30% oxygen or mechanical ventilation) had a modified room air challenge test performed between $36^{0/7}$ and $36^{6/7}$ weeks [2]. Those who failed the test (or who required CPAP with ≥30% oxygen or mechanical ventilation) were classified as "Failed Room Air Challenge test".

Risk Factors:

Gestational age was determined by the date of last menstrual period and early ultrasounds performed before 24 weeks' gestation. Small for gestational age (SGA) infants had birthweight-for-gestational age z scores <−1.29 using the growth curves from Fenton and Kim [28]. Serious intraventricular hemorrhages (sIVH) were defined as grades 3 or 4 intraventricular hemorrhage (using the four-level grading system) [29]. Necrotizing enterocolitis (NEC) was defined as Bell's classification II or greater (this included NEC that was treated medically or surgically) [30]. Spontaneous intestinal perforations (SIP) were diagnosed by either the presence of a pneumoperitoneum on abdominal X-ray without signs of NEC or by the surgeon at the time of laparotomy. Serious pulmonary hemorrhages were defined by the presence of frank blood in the tracheal secretions, a sudden need for increased respiratory support, and chest X-ray changes. Severe retinopathy of prematurity (sROP) was defined as retinopathy requiring laser or bevacizumab treatment.

Statistical analysis

Stata software (Release 17.0; StataCorp LP, College Station, Texas) was used for all statistical analyses. Chi-squared, Mann-Whitney *U* Test and Student's t-tests were used to compare groups for categorical and parametric variables, respectively. We used an analysis of variance (ANOVA), a Kruskal-Wallis equality of populations rank test, and a Cochran–Armitage test for trend to determine if any of the demographic characteristics (Table 1) or outcomes listed in Table 2 were unevenly distributed among the infants with different lengths of PDA exposure. We created multivariable models to adjust for the possible confounding effects of unevenly distributed demographic characteristics on the relationship between our variable of interest (duration of PDA L-R shunt) and our primary outcome (BPD-PVD). These analyses were conducted with logistic regression using generalized estimating equations (GEE) techniques to account for clustering of infants within mothers. Our results were considered exploratory and were not adjusted for multiple comparisons.

Results:

Three hundred and ten infants <28 weeks' gestation were admitted during the study period. The study population was composed of the 256 infants who survived beyond 36 weeks' PMA (Figure); 151/256 were classified as BPD-RS because they needed respiratory support beyond 36 weeks' PMA; 105/256 were classified as No BPD-RS because they no longer needed respiratory support at 36 weeks. Although our nursery guidelines stated that routine screening echocardiograms to evaluate PH were not needed if infants were not receiving respiratory support beyond 36 weeks, 42/105 of the No BPD-RS infants continued to have echocardiograms performed for PDA follow-up beyond 36 weeks (until final PDA closure). None of the infants with No BPD-RS who were evaluated after 36 weeks had echocardiographic evidence of PH.

Routine screening echocardiograms to evaluate PH were performed in all 151 of the infants with BPD-RS as long as they were receiving respiratory support. The median (IQR) number of echocardiograms performed after 36 weeks was 2 (1, 4). The median (IQR) age of the

last echocardiogram was 48 weeks (IQR: 37-70). Among the infants with BPD-RS, 22/151 (15%) had echocardiographic evidence of BPD-PH beyond 36 weeks.

The 22 infants with BPD-PH differed from those without BPD-PH in several demographic characteristics: birthweight, SGA, duration of intubation, need for dopamine and colloid resuscitation, sROP, duration of PDA L-R shunt exposure, and death (Table 1). It is worth noting that although the 22 infants with BPD-PH were classified as having BPD-RS because they required respiratory support beyond 36 weeks, two of the infants would not have been classified as having BPD if we used either the Jensen definition (BPD grades 1-3) or the Room Air Challenge test definition of BPD (one infant with PH beyond 36 weeks required no respiratory support on the day the infant turned $36^{0/7}$ weeks but needed support again starting after $36^{6/7}$ weeks; one infant passed the Room Air Challenge test despite needing support for longer periods than the test's conditions). Other studies have similarly observed that while late PH, beyond 36 weeks, usually occurs in infants with moderate/severe BPD, PH may even occur in infants with no or mild BPD [(13)].

Among the 22 infants with BPD-PH, 13 had moderate/large PDA L-R shunts that persisted beyond 36 weeks (Table 1): the moderate/large PDA L-R shunts were associated with flow-associated PH in 12/13 infants; in one of the 13 infants, a moderate/large PDA L-R shunt and flow-associated PH was initially observed at 36 weeks but subsequent echocardiograms and a cardiac catheterization during the interval between 36 weeks and the infant's death at 62 weeks were consistent with the diagnosis of PVD. The 9/22 remaining infants had a closed ductus with their BPD-PH and were considered to have BPD-PVD beyond 36 weeks (Table 1).

Among the 10 infants with evidence of BPD-PVD, 6/10 had cardiac catheterizations in addition to their echocardiograms to evaluate their PH; 2/10 developed pulmonary vein stenosis (≤2 vessels) in addition to PH during the neonatal hospitalization; 5/10 received PH directed pharmacotherapy (bosentan with or without sildenafil); and 3/10 died after 36 weeks' PMA.

The 10 infants with BPD-PVD differed from those without BPD-PVD in all the characteristics observed above for BPD-PH except for not having an increased incidence of PDA L-R shunt beyond 36 weeks' PMA (Table 1). The main goal of our study was to examine the associations between increasing durations of exposure to a moderate/large PDA L-R shunt and the development of BPD-PVD. Although increasing durations of moderate/large PDA L-R shunt were associated with an increased incidence of BPD (no matter what definition of BPD was used (Table 2)), we found no association between increasing durations of exposure to a moderate/large PDA L-R shunt and BPD-PVD after 36 weeks in either the total population of infants, with and without BPD-RS (n=256), or in a subpopulation composed only of infants with BPD-RS (n=151) (Table 2).

While most demographic characteristics were similarly distributed among infants with different lengths of PDA L-R shunt exposure, a few characteristics appeared to be unevenly distributed among the PDA exposure groups (Table 2). Therefore, we created multivariable models to examine the potential confounding effects of these characteristics

on the association, or lack of association, between the duration of PDA L-R shunt exposure and the presence of BPD-PVD after 36 weeks (Table 3). After adjusting for the potentially confounding characteristics listed in Table 3, we still did not find an association between the duration of PDA L-R shunt exposure and the presence of BPD-PVD after 36 weeks' PMA.

Among the 10 infants with BPD-PVD, 9/10 had evidence of PVD in the first echocardiographic study performed at 7 days after birth (3 had evidence of PH in the absence of a PDA shunt; 6 had evidence of PH with a PDA bidirectional or right-to-left shunt). Eight of the 10 infants with BPD-PVD had echocardiograms performed between the first week and 36weeks' PMA; 5/8 continued to show evidence of PVD.

Discussion:

We defined late BPD-PH as the presence of PH beyond 36 weeks' PMA in infants diagnosed with BPD-RS. We found the same risk factors for BPD-PH that have been seen in other observational studies that have examined the incidence of BPD-PH [13]: low birthweight, SGA, BPD severity, duration of ventilation, ROP severity, and persistence of a PDA L-R shunt (Tables 1 and 2). In our study, the association between a PDA L-R shunt and BPD-PH appeared to be due to an increased incidence of flow-associated PH from the moderate/large PDA L-R shunts that persisted beyond 36 weeks' PMA. Fifty-nine percent of the infants who still had a moderate/large PDA L-R shunt after 36 weeks' PMA had evidence of flow-associated BPD-PH that disappeared once the PDA was closed.

Prolonged exposure to a PDA's high flow and pressure ultimately induces pulmonary vascular remodeling and PVD in term infants with PDA-congenital heart disease [16, 17]. We hypothesized that the presence of a moderate/large PDA L-R shunt in extremely preterm infants would accelerate the rate of developing PVD during the neonatal hospitalization. However, we found no association between the duration of exposure to a moderate/large PDA L-R shunt and the presence of BPD-PVD in either our univariate analysis (Table 2) or our adjusted multivariable analyses (Table 3). We failed to detect an increased incidence of BPD-PVD even in infants with PDA exposures ≥50 days (median (IQR)=70 (60-79) days) (Table 2). However, this does not mean that longer exposures to a PDA L-R shunt, beyond the nursery hospitalization, might not ultimately lead to PVD if left unchecked. Infants cared for at higher elevations than sea level may also be at increased risk for earlier development of BPD-PVD in the presence of a PDA L-R shunt.

It is interesting to note that 9 of the 10 infants with BPD-PVD had evidence of PVD during the first week after birth and the majority had evidence of PVD on repeated echocardiograms performed before 36weeks' PMA. This is consistent with the hypothesis that late PVD may be a manifestation of events that occur in utero or shortly after birth, rather than a consequence of prolonged exposure to PDA flow during the first few months of life.

There are several limitations to our study. Prior studies have both questioned [31] and supported [32] the ability of echocardiography to evaluate BPD-PH. Echocardiography does not measure pulmonary pressures directly but rather uses blood flow velocities to estimate

pulmonary artery pressures and PH [33, 34]. Since pulmonary artery pressure and pulmonary vascular resistance (PVR) are related to each other (Pressure = Flow x Resistance), elevated PVR is inferred from the estimated elevated pulmonary artery pressures when pulmonary blood flow is not increased. We previously showed that echocardiography can perform well as a screening tool for elevated PVR and BPD-PVD when post-tricuspid valve shunts are absent (accuracy, sensitivity, and PPV = 93%, 91.7%, and 100%, respectively) [27]. Since post-tricuspid valve shunts transmit the systemic pressure to the pulmonary circulation regardless of the presence or absence of PVD, the presence of a purely left to right shunt does not necessarily exclude PVD from being present. Although we classified infants with pure PDA L-R shunts and PH in our study as having flow-associated PH, we feel that this is the most likely diagnosis since in each case the PH disappeared as soon as the PDA was closed. Similarly, even though bidirectional PDA shunts do not always imply elevated PVR, the one infant in our study with a bidirectional PDA shunt beyond 36 weeks that we classified as having PVD also had PVD at cardiac catheterization.

Our study cannot address the incidence of brief transient periods of PH that appear and disappear prior to 36 weeks' PMA since routine echocardiographic screening evaluations for PH were not started until a diagnosis of BPD-RS was made at 36 weeks. In addition, since routine echocardiographic evaluations for BPD-PH were performed only in infants who required respiratory support beyond 36 weeks, infants who did not have BPD-RS were not routinely evaluated for PH and were assumed to have normal pulmonary artery pressures beyond 36 weeks. It is possible that some of the infants who never developed BPD, and never were evaluated for late PH, may have had PH that was missed. However, 42 infants without a diagnosis of BPD-RS had echocardiograms performed beyond 36 weeks (because they needed PDA follow-up) and none of them had any evidence of PH on their follow-up echocardiograms. In addition, we found the same relationships between PDA exposure and the outcomes BPD-PH and BPD-PVD in the subpopulation of infants with BPD-RS, where every infant had echocardiographic evaluations for PH performed beyond 36 weeks, as we did in the total population.

We used data from a single center. Since the incidence of moderate/large PDA and neonatal morbidities differ by center, our results may not be generalizable to centers where the rates differ from ours. Our study was not a randomized controlled trial. As an observational study, it cannot distinguish between causation and association and should be used primarily for hypothesis generation. Even though our analyses were adjusted for potential confounding variables, there may have been unmeasured changes in practice that could have affected our results. In addition, the relatively small size of our study may have made it difficult to detect significant differences for some of our study outcomes. We cannot exclude the possibility that our findings were due to insufficient power. However, our study size was necessarily limited by the small number of infants who develop BPD-PH and BPD-PVD in our nursery.

In conclusion we found that persistent moderate/large PDA L-R shunts can increase the risk of flow-associated BPD-PH when they are present beyond 36 weeks' PMA. On the other hand, persistent moderate/large PDA L-R shunts do not appear to increase the incidence of BPD-PVD found by echocardiography during the neonatal hospitalization.

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Data Availability:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request

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Impact Statement:

- In our study preterm infants (<28 weeks' gestation) with bronchopulmonary dysplasia (BPD) had a 15% incidence of pulmonary hypertension (PH) beyond 36 weeks' postmenstrual age as a comorbidity.
- Moderate/large patent ductus arteriosus (PDA) shunts increased the risk of flow-associated PH when present beyond 36 weeks.
- Although months of prolonged PDA exposure can cause pulmonary vascular remodeling and pulmonary vascular disease (PVD) in term infants with PDA-congenital heart disease, we found no echocardiographic evidence for an association between the duration of PDA exposure and the incidence of late PVD during the neonatal hospitalization in preterm infants with BPD.

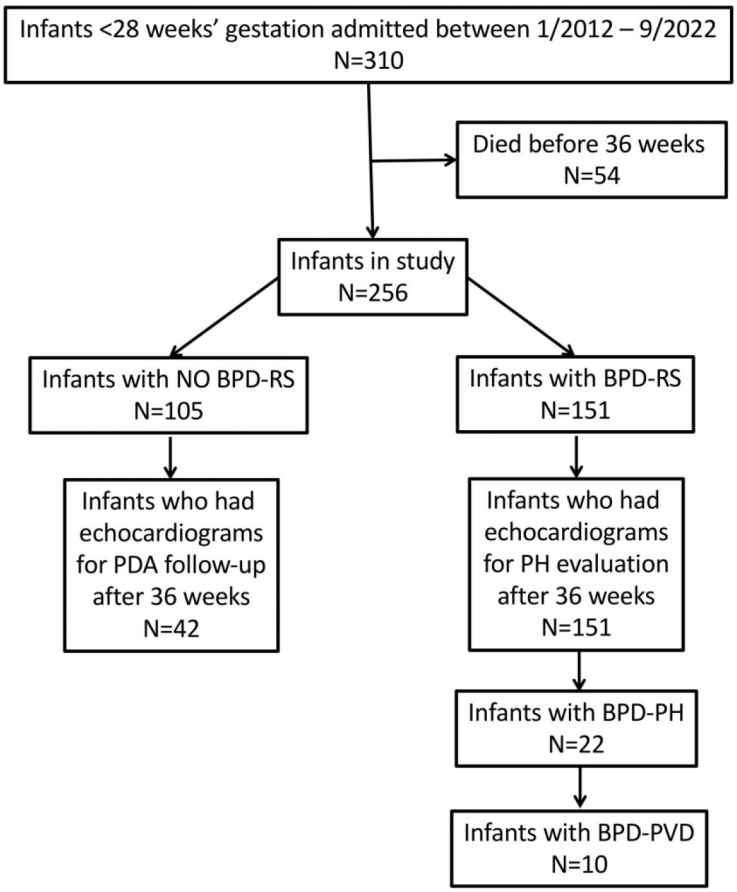

Figure 1: Flow diagram of patient distribution.

BPD-RS: infants who needed respiratory support (cannula, CPAP, or ventilation) beyond 36 weeks' PMA; *PH*: pulmonary hypertension; *BPD-PH*, infants with bronchopulmonary dysplasia-associated pulmonary hypertension; *BPD-PVD*, infants with bronchopulmonary dysplasia-associated pulmonary vascular diseases/disorders.

Table 1:

Distribution of demographic characteristics among infants in the total study population (n=256) who had BPD and pulmonary hypertension (BPD-PH) or BPD and pulmonary vascular disease (BPD-PVD) beyond 36 weeks.

	No BPD-PH (n=234)	BPD-PH (n=22)	No BPD-PVD (n=246)	BPD-PVD (n=10)
Prenatal:				
Year born (m±sd)	2017±3	2017±3	2017±3	2017±3
Multiple gestation - %	30	41	30	40
Preeclampsia - %	23	36	23	40
Maternal diabetes - %	20	18	20	10
Chorioamnionitis - %	13	0	13	0
Antenatal betamethasone ≥24 hours - %	79	73	79	80
Caesarian section - %	68	86	69	80
Delayed cord clamping - %	52	45	55	50
Outborn - %	12	9	11	0
Neonatal:				
Gestation – weeks (m±sd)	26.2±1.1	25.9±1.2	26.2±1.1	25.6±1.3
Birthweight – grams (m±sd)	846±194	647±190 ****	839±197	571±150 ****
Small for gestational age - %	9	45 ****	11	40 *
White - %	37	36	37	50
Male - %	52	55	52	60
5 minute Apgar ≤5 - %	32	55 *	34	40
Days intubated during first 24 days - median (IQR)	2 (0, 11)	20 (1, 24) ****	2 (0, 12)	21 (7, 24) ****
Dopamine ≥10 μgm/kg/min for >24h during first 96 hours - %	11	27 *	11	40 *
Colloid received during first 72 hours [a] - ml/kg - median (IQR)	0 (0, 15)	17 (0, 44) ***	0 (0, 15)	22 (0, 42) *
Bacteremia (culture positive) - %	19	18	19	20
sIVH (grades 3 or 4) - %	4	5	4	0
NEC or SIP during hospitalization - %	10	9	9	0
Pulmonary hemorrhage - %	3	9	3	20
Days exposed to moderate/large PDA [b] - median (IQR)	10 (0, 27)	52 (8, 71) ****	12 (0, 30)	0 (0, 34)
PDA (moderate/large) ≥36 weeks - %	4	59 ****	9	10
PDA ligation or device closure - %	5	27 ***	7	10
ROP requiring laser or bevacizumab - %	12	32 *	13	40 *
BPD-RS [c] - %	55	100 ****	57	100 ***
BPD grades 1-3 (Jensen) [d] - %	53	95 ****	55	90 *
BPD grades 2,3 (Jensen) [e] - %	16	68 ****	24	80 ****

	No BPD-PH (n=234)	BPD-PH (n=22)	No BPD-PVD (n=246)	BPD-PVD (n=10)
Failed Room Air Challenge Test [f] - %	29	91 ****	32	80 ***
Death after 36 weeks - %	0	14 ***	0	30 ****

*, p<0.05

**, p<0.01

***, p<0.005

****, p<0.001

IQR, interquartile range

[a] *Colloid received*: total volume of either packed red blood cells, platelets, or fresh frozen plasma received during 1st 72 hours

[b] *Days exposed to moderate/large PDA*: see Methods: Infants with a constricted ductus at postnatal day 7 (the first echocardiogram) were assumed to have had 0 days of moderate/large PDA exposure during the first 7 days.

[c] *BPD-RS*: infants needing respiratory support (cannula, CPAP, or ventilation) beyond 36 weeks' PMA

[d] *BPD grades 1-3 (Jensen)*: infants with any grade of BPD (1, 2, or 3) as described by Jensen et al (4)

[e] *BPD grades 2,3 (Jensen)*: infants with grade BPD grades 2, or 3 as described by Jensen et al (4)

[f] *Failed Room Air Challenge test*: infants who failed to pass a modified room air challenge test performed between $36^{0/7}$ and $36^{6/7}$ weeks (2).

Table 2:

Distribution of demographic characteristics among infants exposed to moderate/large PDA L-R for different durations in both the total study population (n=256) and the subpopulation of infants who required respiratory support for more than 36 weeks.

	Days exposed to a moderate/large PDA - total study population (n=256)				
	<7 days (n=109)	**7-13 days (n=32)**	**14-28 days (n=44)**	**29-49 days (n=43)**	**≥50 days (n=28)**
PDA exposure – days (median (IQR)	0 (0, 0)	11 (9, 12)	21 (17, 25)	35 (31, 42)	70 (60, 79)
Prenatal Variables:					
Year born (m±sd)	2018±3	2016±3	2017±3	2016±3	2017±3
Multiple gestation - %	30	34	20	35	39
Preeclampsia - %	19	25	20	33	32
Maternal diabetes - %	22	16	13	23	18
Chorioamnionitis - %	16	3	16	12	0
Antenatal betamethasone ≥24 hours - %:	85	66	80	74	75
Caesarian section - %	70	69	64	67	82
Delayed cord clamping - % ****	68	25	50	56	46
Outborn - %	6	19	18	14	11
Neonatal Variables:					
Gestation – weeks (m±sd)	26.4±1.1	26.5±1.1	25.8±1.1	26.0±1.0	26.0±1.0
Birthweight – grams (m±sd)	843±210	879±191	805±188	833±188	744±207
Small for gestational age - % ****	12	3	11	2	36
White - %	38	41	41	28	37
Male - %	57	53	59	37	46
5 minute Apgar ≤5 - % ****	28	50	28	26	60
Days intubated during first 24 days – median (IQR) *	0 (0, 9)	2 (0, 6)	4 (0, 17)	4 (0, 18)	12 (0, 24)
Dopamine ≥10 μgm/kg/min for >24h during 1st 96 hours - %	6	13	20	16	18
Colloid received during 1st 72 hours [a] - ml/kg - median (IQR)	0 (0, 10)	0 (0, 15)	0 (0, 21)	0 (0, 21)	4 (0, 50)

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Bacteremia (culture positive) - %	15	22	25	19	25
sIVH (grades 3 or 4) - %	3	0	5	9	4
NEC or SIP during hospitalization - %	8	6	11	9	21
Pulmonary hemorrhage - % ***	0	13	0	7	11
ROP requiring laser or bevacizumab - %	8	9	18	21	21
BPD-RS [b] - % ***	53	44	64	58	93
BPD grades 1-3 (Jensen) [c] - % ***	51	41	59	58	89
BPD grades 2, 3 (Jensen) [d] - % ***	20	16	34	21	53
Failed Room Air Challenge Test [e] - % ****	21	22	39	35	89
Outcomes:					
BPD-PH - % ****	5	3	5	2	46
BPD-PVD - %	5	3	5	2	4
	Days exposed to a moderate/large PDA among infants with BPD-RS (n=151)				
	<7 days (n=58)	**7-13 days (n=14)**	**14-28 days (n=28)**	**29-49 days (n=25)**	**≥50 days (n=26)**
Outcomes:					
BPD-PH - % ****	9	7	7	4	50
BPD-PVD - %	9	7	7	4	4

*, p<0.05

**, p<0.01

***, p<0.005

****, p<0.001

IQR, interquartile range

[a] *Colloid received*: total volume of either packed red blood cells, platelets, or fresh frozen plasma received during 1st 72 hours

[b] *BPD-RS*: infants needing respiratory support (cannula, CPAP, or ventilation) beyond 36 weeks' PMA

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[c] *3 BPD grades 1-3 (Jensen)*: infants with any grade of BPD (1, 2, or 3) as described by Jensen et al [4]

[d] *BPD grades 2,3 (Jensen)*: infants with grade BPD grades 2, or 3 as described by Jensen et al [4]

[e] *Failed Room Air Challenge test*: infants who failed to pass a modified room air challenge test performed between $36^{0/7}$ and $36^{6/7}$ weeks [2].

Table 3:

Two-variable models examining the odds ratios and 95% confidence intervals (OR (95% CI)) of various durations of exposure to a moderate/large PDA for the outcome pulmonary vascular disease greater than 36 weeks' PMA (BPD-PVD). The two variable models were analyzed with logistic regression using generalized estimating equations techniques to account for clustering within multiple (twin/triplet) births.

	Odds ratios (95% CI) of various durations of exposure to a moderate/large PDA for the outcome BPD-PVD (n=256)				
	<7 days (n=109)	**7-13 days (n=32)**	**14-28 days (n=44)**	**29-49 days (n=43)**	**≥50 days (n=28)**
Two Variable Models examining the OR of PDA duration for BPD-PVD:					
PDA duration plus birthweight	1	1.63 (0.17, 15.8)	1.03 (0.17, 6.30)	0.74 (0.06, 8.33)	0.34 (0.04, 2.62)
PDA duration plus SGA	1	0.91 (0.10, 8.72)	1.0 (0.18, 5.56)	0.70 (0.08, 6.36)	0.42 (0.05, 3.76)
PDA duration plus delayed cord clamping	1	0.59 (0.05, 7.47)	0.94 (0.19, 4.78)	0.48 (0.05, 4.55)	0.73 (0.09, 6.16)
PDA duration plus 5 minute Apgar ≤5	1	0.61 (0.06, 6.52)	1.01 (0.19, 5.45)	0.54 (0.06, 4.72)	0.71 (0.09, 5.90)
PDA duration plus Colloid received during 1st 72 hours	1	0.71 (0.08, 6.69)	1.03 (0.18, 5.78)	0.52 (0.06, 4.67)	0.75 (0.09, 6.45)
PDA duration plus Dopamine ≥10 μgm/kg/min for >24h during 1st 96 hours	1	0.54 (0.05, 5.90)	0.65 (0.10, 4.13)	0.36 (0.03, 4.08)	0.54 (0.07, 4.38)
PDA duration plus pulmonary hemorrhage	1	0.20 (0.02, 1.83)	0.99 (0.18, 5.34)	0.23 (0.01, 6.41)	0.28 (0.04, 2.07)
PDA duration plus number of days intubated during first 24 days	1	0.46 (0.06, 3.78)	0.52 (0.10, 2.70)	0.21 (0.01, 3.00)	0.22 (0.02, 2.19)
PDA duration plus ROP requiring laser or bevacizumab	1	0.64 (0.08, 5.18)	0.76 (0.17, 3.43)	0.36 (0.03, 3.89)	0.56 (0.08, 4.10)
PDA duration plus BPD grades 2, 3 (Jensen)	1	0.79 (0.09, 7.24)	0.63 (0.11, 3.52)	0.46 (0.04, 5.11)	0.32 (0.03, 3.11)

*, p<0.05

**, p<0.01

***, p<0.005

****, p<0.001

The ORs in the table are for the variable of interest: *PDA duration*. None of the PDA durations had an OR that was statistically significant.

The ORs for the second variable in the two variable models are not shown in the table. The following second variables were significantly associated with the outcome BPD-PVD and independent of the variable *PDA duration*: Birthweight (grams) (0.98 (0.98, 0.99) ****; SGA (6.37 (1.68, 24.2)) **; Dopamine ≥10 μgm/kg/min for >24h during 1st 96 hours (6.10 (1.40, 26.6)) *; Pulmonary hemorrhage (22.4 (2.38, 210.4) **; Number of days intubated during first 24 days (1.15 (1.05, 1.26)) ***; ROP requiring laser or bevacizumab (5.31 (1.47, 19.2)) **; BPD grades 2, 3 (Jensen) (15.1 (2.99, 75.9)) ****.