NEONATAL HEMODYNAMICS Research Centre

# Case Report

## Impact of Bronchopulmonary Dysplasia and Pulmonary Hypertension on Ventricular Septal Defect Hemodynamics.

Jose Aldana and Luc Mertens.

Division of Cardiology, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada.

**Key physiological insight/learning points:**

A large VSD produces equilibration of LV and RV pressures, but the direction and amount of flow is dictated by the difference between SVR and PVR.

Elevated PVR limits the VSD shunt volume. In the context of low PVR, the volume of left-to-right shunt will be larger, leading to increased pulmonary blood flow, increased LV volume load and may cause high-output heart failure.

Chronic exposure of the pulmonary vascular bed to increased pulmonary blood flow and systemic pressure in the context of a large VSD leads to pulmonary vascular disease.

The impact of BPD-PH and elevated PVR in VSD shunt hemodynamics should be assessed as it will impact the volume of shunt.

### Background:

We present a case of a premature infant with bronchopulmonary dysplasia - associated pulmonary hypertension (BPD-PH) and a large ventricular septal defect (VSD) who underwent a Pulmonary Artery Banding (PAB). Following the PAB, the infant had a very unstable course mainly due to the underlying respiratory disease. This case highlights the impact that BPD-PH can have on VSD hemodynamics by limiting the volume of intracardiac shunt.

BPD-PH occurs in 30-40% of extremely low birthweight infants and is associated with short and long-term negative outcomes such as increased use of respiratory support, poor neurodevelopmental outcome, increased mortality and accelerated decline in cardiopulmonary function in adulthood.(1–3) BPD-PH results in alveolar diffusion impairment and abnormal vascular changes which lead to increased pulmonary vascular resistance (PVR).(4) Assessment of PVR is essential when evaluating shunting across a large VSD as the volume of shunting will be determined by the relative difference between PVR and systemic vascular resistance (SVR).(5) Thus, the ratio of PVR-SVR is very important to take into account when clinically evaluating a patient with a large VSD. Increased PVR will limit the degree of shunting and clinically distinguishing between the effects of lung disease and the effect of pulmonary overcirculation can be challenging.

### Birth History:

The infant was delivered at 27 weeks by C-section due to severe in-utero growth restriction (IUGR) and abnormal Dopplers in the context of advanced maternal age and pregnancy induced hypertension. Birth weight was 415 g. Infant had Apgars of 3, 3 and 9 at 1, 5 and 10 minutes after birth and was intubated in the delivery room. Cord gases were normal and there was no concern for genetic abnormalities.

### Medical History:

The infant required mechanical ventilation for 20 days during the first month after birth during which a course of systemic steroids was administered. Following extubation, the infant required high-level of non-invasive positive pressure respiratory support and received a

course of inhaled steroids. The infant remained on non-invasive respiratory support and was dependent on continuous positive airway pressure (CPAP) by 36 weeks of corrected gestational age. The history was negative for other major complications including necrotizing enterocolitis, intraventricular hemorrhage, or retinopathy of prematurity. There was no history of postnatal failure to thrive.

The echocardiograms during the first weeks after birth documented a large perimembranous VSD (PMVSD), and subsequently the closure of the PDA (closed within 3 weeks after birth with history of pharmacological treatment). By 41 weeks corrected gestational age (around 4 months), the cardiorespiratory support consisted in high-flow nasal cannula, $FiO^2$ of 0.35, and diuretics. Chest x-ray at this time-point showed signs of chronic lung changes, areas of atelectasis alternating with areas of hyperinflation and increased vascular markings **(image 1)**. This clinical condition was thought to be significantly due to the large VSD resulting in high pulmonary blood flow (Qp), thus decision was made to undergo a PAB with the thought to decrease Qp. The pre-intervention echo showed a large PMVSD with bidirectional shunting (left to right in systole, with right to left shunting in diastole), no LA/LV dilatation but RV dilation and hypertrophy, pulmonary artery (PA) mid-systolic notching, flat septum in systole and diastole (with a right arm systolic blood pressure of 81mmHg), and a foramen ovale with bidirectional shunt **(image 2)**. The systolic ventricular function was normal. The PAB was done at 41 weeks of corrected gestation with a weight of 2.2 kg.

## Hemodynamic Consultation:

The course following the PAB was marked by pulmonary hypertension and vasoreactivity leading to cardiorespiratory instability. The infant required a long post-operative intensive management including 45 days of mechanical ventilation, one month of inhaled nitric oxide which was transitioned subsequently to sildenafil, and prolonged course sedatives, opioids, and muscle relaxation. The Pulmonary Hypertension service was consulted finally during this post-operative period.

Post-PAB serial echocardiograms showed a low gradient across the PA band raising the concern for persistently elevated PVR and distal PA pressure or a loose band. Finally, three weeks after the procedure a cardiac catheterization was performed to clarify the hemodynamics. These data showed a baseline elevated PVRi, a balanced Qp:Qs, a low PAB gradient (9mmHg) and fully saturated pulmonary venous blood **(table 1)**. The lowest PVRi was obtained while giving high $FiO^2$ and 5 ppm iNO (condition 2) which double the Qp:Qs, suggesting responsiveness to oxygen. Post catheterization, the infant remained on respiratory support, oxygen, sildenafil and diuretics. Over the following months, the PAB gradient gradually increased (from 16 to 40s mmHg) and the shunt through the VSD became all left to right throughout the cardiac cycle. During this time the biventricular function remained within normal limits.

## Imaging Findings

### Image 1. Pre-surgical chest X-ray:

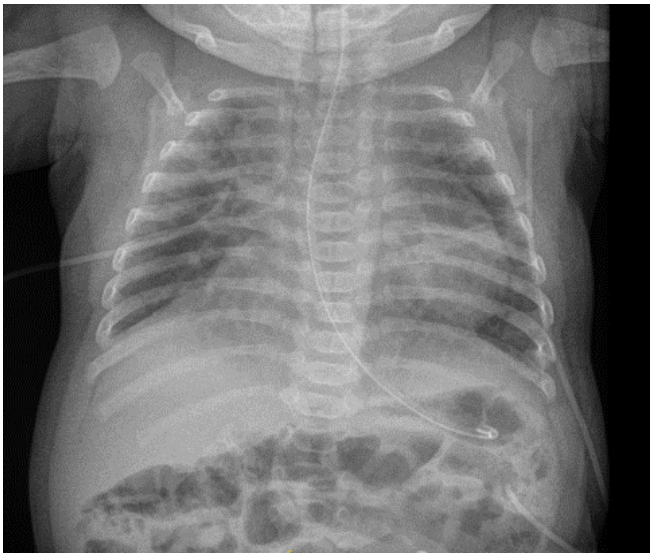
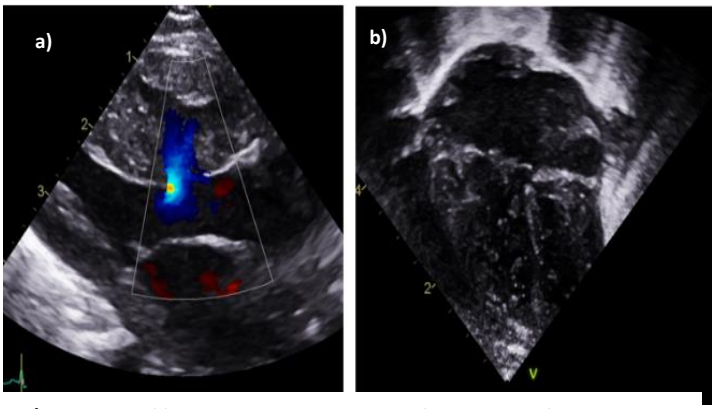
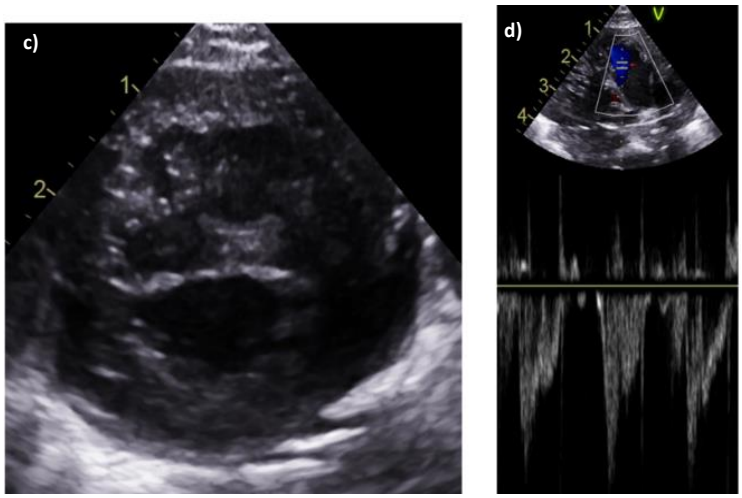


Image 2. Pre-surgical echocardiogram.




**a)** Parasternal long axis view. Large VSD shunting R-L during diastole and RV hypertrophy.
**b)** Apical 4-ch view. RV hypertrophy and dilation.




**c)** Parasternal short axis view. RV hypertrophy and dilation, septal flattening.
**d)** Pulsed-wave Doppler envelop at the level of pulmonary valve illustrating mid-systolic notching.

Table 1. Cardiac Catheterization post PAB, hemodynamic data:

| Site | Condition 1: Baseline $FiO^2$ 0.25, iNO 5ppm | | Condition 2: Test $FiO^2$ 0.8 and iNO 5ppm | |
|---|---|---|---|---|
| | Pressure (mmHg) | Saturations (%) | Pressure (mmHg) | Saturations (%) |
| RA (m) | 5 | | 5 | |
| RV (s/edp) | 51/8 | | 50/8 | |
| RPA (s/m) | 44/27 | 74 | 41/25 | 84 |
| LPA (s/m) | 40/27 | 71 | 37/23 | |
| Pulmonary veins | | 93-99 | | 100 |
| LA (m) | 5 | | 5 | |
| LV (s/edp) | 52/7 | | | |
| **Calculations** | | | | |
| Qp:Qs | 1.1:1 | | 2.1:1 | |
| PVRi | 5.6 | | 3.6 | |

**Abbreviations:** edp, end diastolic pressure; iNO, inhaled nitric oxide; m, mean pressure; PAB, pulmonary artery band; ppm, part per million; PVRi, pulmonary vascular resistance index; Qp:Qs, pulmonary to systemic flow ratio; s, systolic pressure.

## Follow up/ Outcome:

The level of respiratory support was able to be weaned gradually and the pulmonary vasoreactivity improved. Finally, the infant was discharged to a Community Hospital at the age of 9 months (6 months corrected) with low flow oxygen and BiPAP during sleep, sildenafil, diuretics and with post-pyloric feeds. The infant will eventually undergo another cardiac catheterization to assess the timing for VSD closure.

## Discussion

We have presented a case of a premature infant with BPD-PH and a large VSD that underwent a PAB after which had a very unstable course secondary to the respiratory disease. The case illustrates the importance of considering the impact of the underlying BPD-PH on the VSD hemodynamics.

The infant had several morbidities that are associated with the development of BPD-PH including: IUGR, low birthweight, and prolonged course of mechanical ventilation.(6) These factors lead to abnormal airway growth, impaired alveolarization, simplified alveoli, and abnormal pulmonary vasculature which results in chronically elevated PVR.(4,7) These factors likely contributed to the chronic need of respiratory support. In addition, the VSD was considered a significant contributor to the clinical condition due to pulmonary overcirculation. Interestingly, the post-operative course and the post PAB catheterization data suggest that the main problem was the respiratory disease.

The physiology of a VSD is influenced size of the defect and the relationship of the PVR and SVR. Thus, the PVR to SVR relationship determines the volume and direction of flow across the defect as illustrated by the fact that soon after birth infants with a large VSD are asymptomatic because PVR remains high, but after the first weeks following birth with the gradual drop in PVR an increased left to right shunting occurs.(8) If the left-to-right shunt is large leads to pulmonary overcirculation and LV volume loading which can manifest with heart failure symptoms. In addition to the volume load, a large VSD exposes the RV and pulmonary vascular bed to systemic pressure. Thus, in conjunction and over prolonged period of time if a significant VSD is left untreated, there will be remodelling of the pulmonary vasculature (medial hypertrophy and intimal proliferation) leading to increased PVR and pulmonary hypertension, however this complication especially occurs after 1 year of age.(9,10)

As illustrated in this case, it is challenging to determine whether the main contributing factor to the clinical condition was mainly due to BPD-PH or the VSD. Prior to the PAB, the infant underwent serial echocardiograms to assess the hemodynamic consequences of the BPD-PH and the large VSD. The echocardiogram markers that suggested presence of pulmonary hypertension included: PA systolic notching, RV hypertrophy and dilation and septal flattening.(11) The RV hypertrophy leads to decreased RV compliance and higher RV diastolic pressure which explain the diastolic R-L VSD shunt and the right to left shunt at atrial level. Finally, the flow in the pulmonary artery was not significantly elevated and the LA/LV were not dilated indicating that the L-R shunt was not very significant. The anatomical size of the VSD was classified as large because it was the same size as the aortic valve annulus.(12) In conjunction, these echocardiography markers suggested that the main problem for the patient was BPD-PH rather than a large L-R shunt caused by the VSD. The post-operative course supported this rationale as the period following the PAB was characterized clinically by significant pulmonary vasoreactivity and protracted need for invasive respiratory support. In addition, despite having an anatomically well seated PAB, the serial post-operative scans showed a low gradient across the band suggesting persistently elevated PVR and elevated distal PA pressures.

This suspicion was confirmed by post PAB (around 3 weeks post procedure) cardiac catheterization **(table 1).** The catheterization data showed elevated PVR and a balanced Qp:Qs with a low gradient across the PAB. The hemodynamic assessment was consistent with pre-capillary PHTN based on elevated mean pressure in the branch PAs distal to the PA band, low LA pressure, and elevated PVRi (5.6 WU*m2) at baseline.(13) The vasoreactivity testing, which included high oxygen (0.8) and iNO (up to 40ppm), documented the highest Qp and lowest PVRi with the use of oxygen. In summary, the invasive hemodynamic data indicated that the increased PVR was the main factor resisting Qp.

Finally, over the course of following weeks the gradual increase of the PAB gradient on subsequent echocardiograms suggested that PVR was decreasing. The infant was able to be weaned to a respiratory support that allowed transitioning to a hospital closer to the family's home and subsequently to home.

In conclusion, the presence of BPD-PH and consequently elevated PVR significantly influenced the VSD hemodynamics and significantly impacted the course after the PAB highlighting the important relationship between the cardiovascular and respiratory systems. Pre-surgical cardiac catheterization might be useful to decide timing of intervention but needs to be considered against the potential risks.

REFERENCES:

1. Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro R V, Thomas KC, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics. 2007 Dec 1;120(6):1260–9.
2. Madden BA, Conaway MR, Zanelli SA, McCulloch MA. Screening Echocardiography Identifies Risk Factors for Pulmonary Hypertension at Discharge in Premature Infants with Bronchopulmonary Dysplasia. Pediatr Cardiol. 2022;
3. Duke JW, Lewandowski AJ, Abman SH, Lovering AT. Physiological aspects of cardiopulmonary dysanapsis on exercise in adults born preterm. J Physiol. 2022 Feb 1;600(3):463–82.
4. Hansmann G, Sallmon H, Roehr CC, Kourembanas S, Austin ED, Koestenberger M. Pulmonary hypertension in bronchopulmonary dysplasia. Pediatr Res. 2021 Feb 1;89(3):446–55.
5. Backer CL, Eltayeb O, Mongé SC, Mazwi ML, Costello JM. Shunt Lesions Part I: Patent Ductus Arteriosus, Atrial Septal Defect, Ventricular Septal Defect, and Atrioventricular Septal Defect. Pediatr Crit Care Med. 2016;17(8 Suppl 1):S302–9.
6. 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 Jun 1;23:27–32.
7. Hilgendorff A, Apitz C, Bonnet D, Hansmann G. Pulmonary hypertension associated with acute or chronic lung diseases in the preterm and term neonate and infant. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart. 2016 May;102(Suppl 2):ii49–56.
8. Shaddy RE, Penny DJ, Feltes TF, Cetta F, Mital S. Moss and Adams' heart disease in infants, children, and adolescents : including the fetus and young adult.
9. Kozlik-Feldmann R, Hansmann G, Bonnet D, Schranz D, Apitz C, Michel-Behnke I. Pulmonary hypertension in children with congenital heart disease (PAH-CHD, PPHVD-CHD). Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart. 2016 May 1;102 Suppl 2:ii42–8.
10. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Vol. 53, The European respiratory journal. NLM (Medline); 2019.
11. Koestenberger M, Apitz C, Abdul-Khaliq H, Hansmann G. Transthoracic echocardiography for the evaluation of children and adolescents with suspected or confirmed pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric

pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and D6PK. Heart. 2016 May 1;102:ii14–22.

12. Lai W. Echocardiography in pediatric and congenital heart disease : from fetus to adult.

13. Hansmann G, Koestenberger M, Alastalo T-P, Apitz C, Austin ED, Bonnet D, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Hear Lung Transplant. 2019 Sep;38(9):879–901.