

## **Pulmonary Vein Stenosis in an Infant with Bronchopulmonary Dysplasia and Partial Anomalous Pulmonary Venous Circulation: Is This Double Trouble?**

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### **Introduction:**

Pulmonary vein stenosis is a rare but emerging condition in ex-preterm infants who are diagnosed with bronchopulmonary dysplasia (BPD) with or without pulmonary hypertension (PHTN). This new entity has an unpredictable natural history with worse outcome when its earlier in onset and bilateral in nature (1). While primary pulmonary vein stenosis has a known association with other cardiac defects especially septal defects (2), progressive pulmonary vein stenosis in the setting of a partial anomalous pulmonary venous return (PAPVR) is a rare occurrence. Here, we highlight a case of progressive pulmonary vein stenosis in an ex-preterm infant with bronchopulmonary dysplasia who also had PAPVR. With markedly variable diagnostic threshold for pulmonary vein stenosis (PVS), for this case report we defined PVS as mean pressure gradient greater than 2mmHg using doppler echocardiogram (3).

### **Case presentation:**

We present a female infant born at 24 weeks gestational age to a 31 year old G10A9 mom. This spontaneously conceived pregnancy was complicated by essential hypertension and preterm labor that was managed with betamethasone and magnesium sulphate. The infant's birth weight was 700 grams (82<sup>nd</sup> centile). Her Apgar scores were 4, 7 and 8 at 1, 5 and 10 minutes respectively. She required intubation by seven minutes of life due to increasing oxygen (FiO<sub>2</sub>) needs of 0.8.

### **Clinical Course in Neonatal Period**

In the Neonatal Intensive Unit (NICU) the infant was managed for issues related to extreme prematurity. She was initiated on high frequency oscillation (HFO) ventilation and given surfactant with good response. She has umbilical arterial line and a low-lying umbilical vein (UV) catheter. On 5<sup>th</sup> day of life she developed progressive abdominal distension, with hemodynamic instability consisting of diastolic hypotension, oliguria (0.8-1.1ml/kg/hr), worsening metabolic acidosis along with anemia and thrombocytopenia.

A neonatal hemodynamic consultation was requested. A targeted neonatal echocardiogram (TNE) discovered a large hepatic cystic mass with possible inferior vena cava (IVC) compression consistent with intrahepatic UVC extravasation. This UV catheter was replaced with an alternate central line and supportive management with normal saline bolus, packed red blood cell and platelet transfusion which resulted in satisfactory stabilization of hemodynamic parameters.

The other TNE findings included a normal cardiac structure, a large patent ductus arteriosus (PDA) 2.1mm in size, shunting left to right with a peak gradient of 4.6mmHg suggesting near systemic pulmonary pressures. There were no echocardiographic markers suggesting hemodynamic significance of PDA. In this initial study – all four pulmonary veins appeared to drain into left atrium.

Her respiratory status remained an ongoing concern requiring escalation of support to a high frequency jet ventilator (HFJV) by second week of life. She received two courses of Dexamethasone (Course 1 at DOL 14 and course 2 at DOL 43). She was extubated and gradually weaned to high flow nasal canula at 5 litres/minute on 0.25-0.30 FiO<sub>2</sub> by 36+5 weeks gestational age. She received a diagnosis of moderate to severe BPD at 36 weeks corrected and continue to demonstrate significant respiratory support needs till term corrected.

### **Echocardiographic Assessments**

The infant had three echocardiographic assessments in the first 3 weeks of life, including the first one mentioned above, during her acute deterioration. The subsequent assessments continued to demonstrate a PDA and estimated pressures based on PDA gradient to be 80-90% of systemic.

She was assessed for BPD associated pulmonary hypertension at 36 weeks corrected which revealed systemic-suprasystemic pulmonary hypertension as evidenced by moderate bidirectional PDA (71% of cardiac cycle is left to right shunt) with flattened septal curvature and mild right atrial and ventricular dilation with preserved cardiac systolic function. Note was made of left upper pulmonary vein (LUPV) stenosis with mean gradient of 7mmHg. Rest 3 pulmonary veins appeared to be normal. Pediatric Cardiology closely followed clinical and echocardiographic course of this infant. Following a course of Aldactazide, she was eventually weaned to Low flow oxygen by DOL#95 at 37+4weeks corrected gestational age. Due to CO<sub>2</sub> retention and rising needs to maintain oxygen saturations above 92%, the infant needed escalation of respiratory support to NIPPV/CPAP. She required multiple courses of diuretics for management of pulmonary hypertension in the setting of PVS associated with severe BPD. Serial echocardiogram showed progression of pulmonary vein stenosis (Table 1) with LUPV becoming almost atretic (Figure 1A) by 40weeks corrected age and additional development of left lower pulmonary vein stenosis (LLPV) (Figure 1B). Quaternary referral center with surgical cardiac unit was consulted and she was deemed eligible for immediate intervention with dilatation of the stenotic veins.

### **Cardiac Catheterization Findings and Procedural Interventions**

At the quaternary referral center, she underwent cardiac catheterization at 42+5 weeks corrected age which revealed severely stenosed and almost atretic LUPV that failed dilatation as well as mild to moderate stenosis of LLPV with successful balloon dilatation. The Doppler flow indicating RUPV draining into LA that was noted in initial echoes could not be confirmed by cardiac catheterization. Instead a moderate-severe stenotic right upper pulmonary vein was found to drain into the Superior Vena Cava (SVC) making it PAPVR anomaly. Additionally, an accessory right pulmonary vein was noted to drain into the left atrium. The right lower pulmonary vein was noted to have a normal laminar flow. Parents were counselled on the guarded nature of the prognosis given that three pulmonary veins were significantly affected along with PAPVR anomaly and early presentation with significant pulmonary hypertension. Palliative care options were discussed given the significant pathology. Parents chose to pursue a 'Do Not Resuscitate (DNR) 'plan that excluded use of chest compression and medication in the event of a cardiac

arrest. Infant continued to have serial echocardiographic assessment with stable PVS and pulmonary hypertension. She had a reattempt for balloon dilatation of the atretic LUPV which was unsuccessful again. She was subsequently discharge home after 7months stay in the hospital on High Flow 4litres/minute at 25% FiO2. She never received pulmonary vasodilators given her lower FiO2 requirements to maintain saturations above 92% and relatively stable pulmonary hypertension.

### Post Discharge Clinical Course:

Following her hospital discharge, she had three hospital visits to the local emergency department due to respiratory distress needing escalation in respiratory support within the first 9months of her life. She was found to have frequent hypoxemia to 80% oxygen saturations on High Flow of 4l/min that was associated with agitation/crying/clinical care as well as tachypnea and increased work of breathing leading to re-admission to Pediatric Critical Care Unit (PCCU) each time. Other than the significant pulmonary hypertension suggested by bidirectional PDA shunt, echocardiogram also demonstrated re-stenosis of LLPV and RUPV along with SVC stenosis with the first two re-admissions. She was transferred to quaternary center for procedural intervention consisting of balloon dilatation and stenting of LLPV and balloon dilatation of both RUPV and SVC. The last admission at 7months corrected age and subsequent follow up cardiac clinic visits revealed stable PVS but persistence of significant pulmonary hypertension with adequate cardiac function. There were no infectious etiology or chest radiograph abnormalities associated with any of these readmissions. She had 2-3weeks stay at PCCU with each of those admissions. At present, she is 9months corrected age with history of procedural interventions for PVS on four occasions thus far and has been actively followed by home palliative care team with stable clinical course and remains on High Flow 4l/min. She continues to have adequate weight gains following enteral nutrition through G-tube. She has monthly cardiac appointments and weekly follow up by palliative care team.

**Table 1: Serial trend in the Echocardiographic parameters prior to procedural intervention**

<b>Pulmonary vein gradient prior to surgical intervention</b>	<b>DOL 5</b>	<b>36weeks CGA</b>	<b>38weeks CGA</b>	<b>40weeks CGA</b>
LUPV, mmHg	0.21	7	12.5	~ 1, almost atretic with minimal flow
LLPV, mmHg	0.27	1	2.2	2.4
Presumed RUPV, mmHg	0.18		0.89	0.77
RLPV, mmHg	0.24	0.7	0.82	0.35
PDA size and shunt direction	Large PDA with left to right shunt	Moderate PDA bidirectional shunt	Moderate PDA bidirectional shunt	Moderate PDA bidirectional shunt
Right chambers	RA and RV normal size	RA/RV mild dilatation	RA/RV moderate dilatation	RA/RV moderate dilatation
TAPSE, cm	0.50	1.1	n/a	n/a
RV FAC, %	37	44	45	37

Abbreviations: CGA- corrected gestational age, DOL- Day of life, LUPV- Left Upper Pulmonary vein, LLPV- Left Lower Pulmonary vein, RUPV- Right Upper Pulmonary vein, RLPV- Right Lower Pulmonary vein, PDA- Patent Ductus Arteriosus, RA- Right Atrium, RV- Right Ventricle. TAPSE - Tricuspid Annular Plane Systolic Excursion, FAC-Fractional Area Change

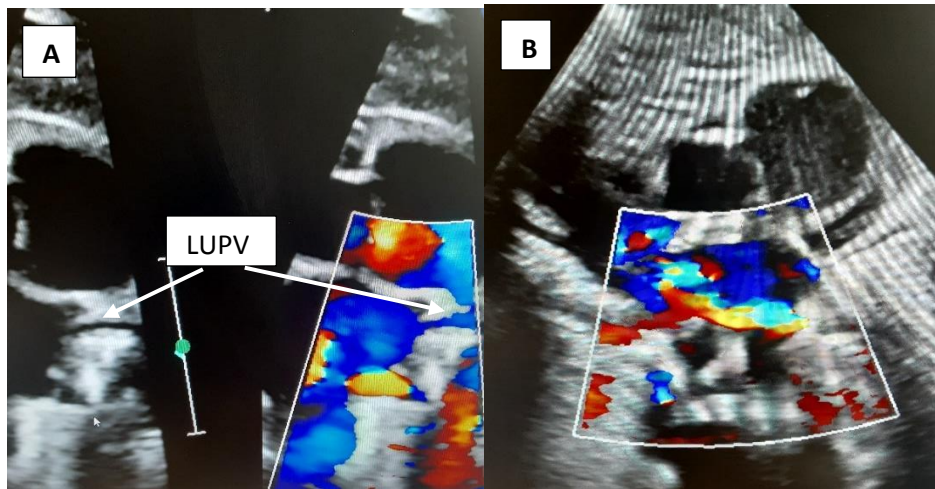


Figure 1: 1A shows severe stenotic almost atretic LUPV and 1B is the crab view showing almost absent flow in the LUPV and turbulent flow in LLPV suggesting PVS. There appears to be a flow where RUPV should drain into Left atrium.

## Discussion:

Pulmonary vein stenosis (PVS) is a rare but serious complication of premature infants with Bronchopulmonary dysplasia (BPD). It is a progressive disease with 5-year survival rate being less than 50% (1, 4). This has led to increasing vigilance by the neonatal physicians towards its earlier detection despite its variable presentation. The median age of diagnosis of PVS in preterm infants ranged from 5-7.4 months across literature with only 20% diagnosed before NICU discharge (5, 6, 7). The widespread availability of bedside echocardiogram has made detailed screening for PVS in the high-risk preterm infants possible with increasing detection rate over the last one decade. Approximately half of the pediatric patients with PVS also have associated cardiac defect (2). Here we have described a rare association of extreme prematurity with moderate-severe BPD and PAPVR contributing to the increased risk for development of PVS. To the best of our knowledge this association has not been reported previously in literature. Our report, summarizes echocardiographic findings, details of clinical course, management plans associated with this rare disease entity as there is limited information about the clinical trajectory of this disease process.

It is estimated that in 30-80% of cases of PVS, there are other associated cardiac defects (8-10). This is mostly left to right shunting lesions like Atrial Septal defect, Ventricular Septal defect, Atrio-Ventricular septal defect, and PDA. But it can also be seen in conjunction with all major type of congenital cardiac malformations (2). An association of pulmonary venous agenesis with PAPVR is postulated to result from abnormal incorporation of the common pulmonary vein into the left atrium in the later stages of cardiac development (11). During the 4<sup>th</sup> week of the embryonic period, there is a common pulmonary venous out pouching that develops from the posterior part of the primordial left atrium. This out pouching engages both pulmonary and systemic venous system initially. With normal cardiac development this connection separates into two independent venous systems namely pulmonary and systemic venous system and eventual formation of 2 right-sided and 2 left-sided pulmonary veins that enter the smooth portion of the posterior left atrium (11). Failure of this process may result in persistence of the connections of the pulmonary veins to the systemic venous system leading to the various forms of partial or total anomalous pulmonary venous return. It has been postulated that abnormal incorporation of the common pulmonary vein into the left atrium in the later stages of cardiac development can result in

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primary PVS. This is suggested to be a neo-proliferative process and therefore may not be evident at birth but could progress later (11,12).

Our case showed progressive nature of PVS needing multiple procedural interventions. Both PAPVR and BPD could have simultaneously accelerated the progression of PVS in our case. Bilateral, multiple vein involvement, presentation before 6 months of age and recurrent stenosis despite intervention suggest aggressive disease progression and poor prognosis for survival (1, 13). The one-year mortality rate reaches 80% when  $\geq 3$  veins are affected. (1, 2, 14-18). The upstream effect of the progressive pulmonary vein disease leads to pulmonary hypertension and right ventricular dysfunction. This can manifest as persistent and frequent hypoxemia, tachypnea, increased work of breathing, unexplained increase in ventilatory and oxygen support (5, 14). These were the presentations that our case manifested at each of the emergency visit leading up to re-admissions. The lability of the oxygen saturations is more in keeping with the clinical manifestation of pulmonary hypertension in our case though the exact cause for this sudden lability could not be delineated.

There is increasing evidence that the left sided pulmonary veins are more affected than the right sided ones, which is noted in our case as well (6, 21-23). The explanation for this observation is unclear. But it's being proposed that since supine position is the most preferred position in infants, the possible compression of the left pulmonary veins against the heart and the spine could potentially lead to stenosis. While others suggest an increased volume of blood shunting to the left pulmonary artery due to PDA and the resultant increased blood circulating in the left lung leading up to vascular endothelial injury could be a contributing factor (1).

Echocardiogram is generally sufficient to diagnosis PVS and remains the first line imaging modality. Although echocardiogram allows bedside assessment and is easily accessible in many centers, inadequate acoustic windows in these extreme preterm infants on ventilatory support limits its diagnostic yield both in the diagnosis of PVS and PAPVR (6). Furthermore, less than 20% of PVS is typically detected before discharge from the NICU and most infants have a median of 3–5 echocardiograms before diagnosis is made (7). Hence cardiac catheterization/angiogram remains the gold standard for diagnostic purposes. In our case, the right accessory pulmonary vein was mistaken for RUPV in all of the echocardiograms performed to assess pulmonary veins missing the draining of RUPV into the SVC and (21) the development of stenosis in RUPV. This again highlights the limitation of echocardiography in diagnosis of PAPVR spectrum. Both Pediatric Pulmonary Hypertension Network and American Heart Association and American Thoracic society collectively recommends evaluation of pulmonary veins during echocardiographic assessment for BPD associated pulmonary hypertension at 36 weeks corrected age in all preterm infants with established BPD (24, 25). Detailed re-evaluation of pulmonary veins especially in the context of ongoing pulmonary hypertension in neonates-with established BPD, atypical clinical trajectory or poor response to medical therapy for pulmonary hypertension cannot be over emphasized.

Current medical therapy for PVS is mainly focused on symptomatic management of cardiorespiratory symptoms. Diuretic therapy is the mainstay of treatment for pulmonary venous congestion that ensues due to PVS. Use of pulmonary vasodilators for pulmonary hypertension are controversial in PVS due to the fixed nature of obstruction and therefore potential worsening of pulmonary congestion secondary to its use (3). It is prudent that the use of pulmonary vasodilators should be in conjunction with diuretic therapy in such cases. Definitive management of PVS is surgical and Coles procedure which is suture less technique is the preferred method (2, 6). The goal of this method is to reduce surgical trauma and hence



reduce any stimulus that can worsen the fibroproliferative process leading to re-stenosis. Other procedural interventions include balloon dilatation and stent implantation (2, 26, 27). In refractory cases lobectomy and lung transplantation has been performed. Prognosis is guarded even after surgical intervention with less than 50% chance of survival at 5years. With bilateral vein involvement and development of restenosis needing repeat procedural intervention, and the presence of at least two aggravating factors, namely BPD and PAPVR, that can contribute to progression of PVS and the presence of significant pulmonary hypertension, the prognosis for our case is considered poor. Commonly death is secondary to pulmonary hypertension, recurrent pulmonary infection or hemoptysis (2). Consultation with experts and institutions that have expertise in caring for children with PVS is highly recommended to develop an individualized treatment and follow-up plan. Palliative care could be a reasonable option in cases where quality of life is deemed significantly affected.

## **Conclusion:**

PVS and BPD are morbid diseases that have some pathogenetic and epidemiologically association. Cardiac defects are frequent association with PVS which can further aggravate the pathogenetic process. Association of PAPVR with PVS has not been well described in literature. The combination of PAPVR and BPD could potentially accelerate the progressive nature of PVS making its course unrelenting despite surgical intervention. Routine echocardiographic evaluation has some inherent limitation when assessing PAPVR especially in the presence of accessory pulmonary veins. High index of suspicion, early screening and detection, timely referral is paramount if actual clinical course is out of keeping with the expected trajectory.

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