NEONATAL HEMODYNAMICS Research Centre

Case Report

Persistent pulmonary hypertension of the newborn in a term infant with mitral valve dysplasia: A post-capillary pathogenesis

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Key learning points:

1. Understanding of the underlying pathophysiology of pulmonary hypertension is key to guide treatment and prevent adverse outcomes
2. Pulmonary venous hypertension causing PPHN should be considered in infants with left ventricular structural or functional abnormalities
3. Infants exposed to in-utero lithium should be considered high risk for cardiac defects, despite the absence of congenital anomalies on routine prenatal ultra- sonography.

Background

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical diagnosis, characterized by hypoxia and increased pulmonary vascular resistance, leading to persistence of the right-to-left fetal shunts through the transitional postnatal period[1]. The incidence of PPHN is 0.2% of term livebirths and 2% of preterm births[2]. The etiology of this condition is typically secondary to pre-capillary or capillary pulmonary vasculature pathologies[1]. We present a case of a term infant, exposed to in-utero lithium, who presented at 24 hours of life with hypoxia, and unusual finding of a predominantly post-capillary etiology for PPHN, which was managed using the guidance of targeted neonatal echocardiography (TNE).

Clinical presentation

Female infant, born at 37+5 weeks' gestation with a birth weight of 3480 grams (81.4th centile) via forceps assisted vaginal delivery, to 37 years old, primigravida mother. Pregnancy was complicated by a medical history of Type 1 bipolar disorder, which was treated with lithium (1200 mg per day), as well as diet-controlled gestational diabetes. Maternal serology during this pregnancy was unremarkable, and GBS status was negative. Fetal ultrasound revealed normal anatomy, normal fetal growth, with a slightly prominent stomach (>95th centile) and polyhydramnios only seen on the ultrasound scan 4 days prior to delivery. Fetal echocardiography at 19 weeks' gestation was unremarkable. Family history was negative for congenital heart disease, early myocardial infarction, sudden death, arrhythmias, or need for pacemakers, and/or an implantable cardioverter defibrillator. There was a prolonged rupture of membranes (PROM) for 22 hours.

After delivery, there were no initial concerns regarding postnatal transition and the infant did not require any resuscitation after birth; Apgar scores were 8 and 9 at 1 and 5 minutes of life, respectively. Infant was transferred to the mother-and-baby unit after birth.

At 24 hours of life, the infant developed respiratory distress with decreased oral intake. On clinical examination, infant had tachypnea (respiratory rate 80/min) and increased work of breathing with subcostal indrawing and intermittent grunting. A grade II/VI systolic murmur at the apex was noted with normal peripheral perfusion and no hepatosplenomegaly. Pre- and post-ductal oxygen saturations (SpO_2)

demonstrated a 12-23% difference, with a lower post-ductal SpO2 at 72-82%. The 4-limb blood pressures (BPs) were reassuring with no upper and lower limb BP difference demonstrated. The infant was started on low flow oxygen at 125 cc/min, with improved SpO2 pre/post >95% and was admitted to our neonatal intensive care unit (NICU) for further evaluation and stabilization.

Clinical course

Upon admission to the NICU, in view of worsening tachypnea and work of breathing, the infant was switched to CPAP 5 cmH_2O, and saturations maintained >95% in FiO_2 0.21. Initial capillary blood gas revealed pH 7.25, pCO2 53 mmHg, pO2 37 mmHg, HCO3 23 mmol/L, BE -4.8 mmol/L, and lactate 2.6 mmol/L. Full blood count showed Hb 123 g/L, WBC 20.48, and PLT 274. Chest x-ray on admission revealed cardiomegaly, right lung air bronchograms and perihilar streaking but was otherwise unremarkable (Figures 1.1-1.2). Antibiotics were commenced upon admission following a partial septic screen.

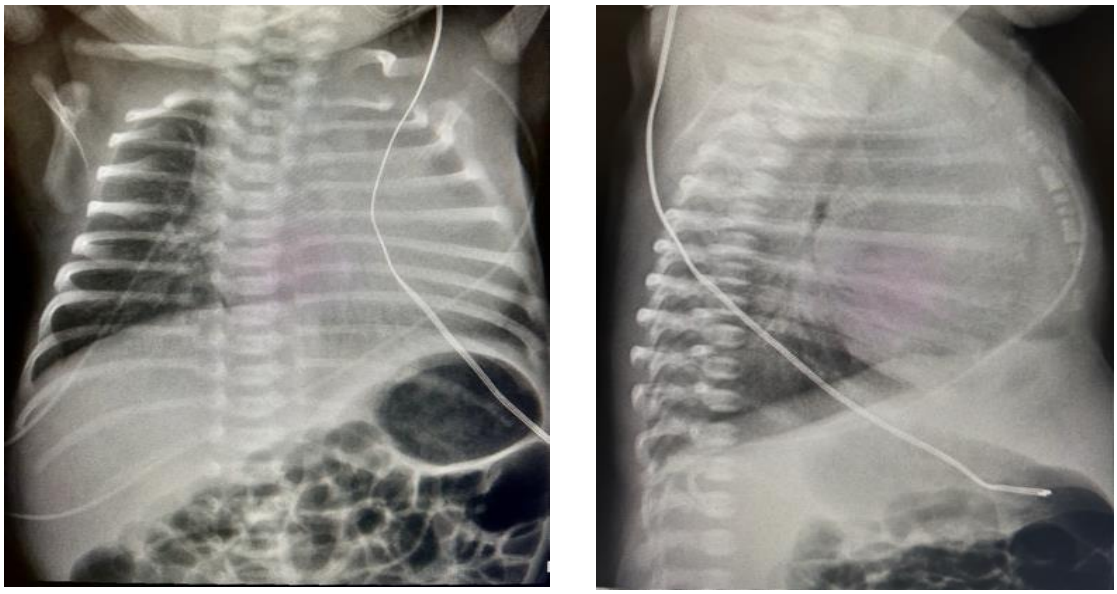

Figure 1. *Chest X-ray demonstrating cardiomegaly seen on admission to the NICU.*

A neonatal hemodynamics consultation was performed at 24 hours of life which revealed a dysplastic mitral valve with significant mitral regurgitation (MR), dilated left atrium (LA), isosystemic pulmonary pressures (estimated by interrogation of the tricuspid regurgitation velocity using continuous-wave Doppler), bidirectional patent ductus arteriosus (PDA) and patent foramen ovale (PFO) shunts, and maintained biventricular systolic function and outputs (Table 1 and Figures 2).

These findings were suggestive of elevated LA pressures secondary to increased LA volume from MR and a post-capillary etiology for pulmonary hypertension. Bidirectional PDA and PFO shunts are suggestive of a mixed pathophysiology with increased PVR in the transitional period. Increased pulmonary resistance can also be expected in the context of pulmonary edema causing hypoxemia, shunting of blood to areas of greater ventilation, pulmonary vasoconstriction, and alveolar edema compressing and distorting capillaries. Subsequently, the infant was started on diuretics (furosemide PO 1 mg/kg BID) to manage pulmonary venous congestion and pulmonary hypertension.

Table 1 – Initial TNE findings	
Echo parameter	Findings
LA	LAESV index: 28.57ml/m^2
MV	Thickened and dysplastic mitral valve Moderate MR via multiple jets: Vmax 2.77m/s, PG max 31.19 mmHg MV annulus: 0.98cm (Z-score -0.8)
LV dimension	LVEDD (M-mode): 2.78cm (Z-score +5.0)
LV function	Ejection fraction (Teich): 62% Fractional shortening: 32% LV s' velocity: 4cm/sec LVOT VTI: 11.28cm LVO 140ml/kg/min
RV dimension	RVEDA: 8.07 cm^2
RV function	TAPSE: 9.9mm RV 4C FAC: 37% RVOT VTI: 5.10 cm RVO: 310ml/kg/min
Pulmonary hemodynamics	RVSP estimated from TR jet: 65mmHg (SBP 63/40 mmHg) RVET/PAAT ratio: 3.5 Flat interventricular septum throughout cardiac cycle
Shunts	PDA: 3.6mm bidirectional shunt PFO: 4mm bidirectional shunt

TNE; targeted neonatal echocardiography, LA; left atrium, LAESV; left atrial end systolic volume, MV; mitral valve, MR; mitral regurgitation, Vmax; maximum velocity measured on continuous wave Doppler, PGmax; maximum pressure gradient, LV; left ventricle, LVEDD; left ventricle end diastolic diameter, LVOT; left ventricular outflow tract, VTI; velocity time integral, LVO; left ventricular output, RV; right ventricle, RVEDA; right ventricular end diastolic area, TAPSE; tricuspid annular plane systolic excursion, RV 4C FAC; right ventricle 4 chamber fractional area change, RVOT; right ventricular outflow tract, RVO; right ventricular output, RVSP; right ventricular systolic pressure, TR; tricuspid valve, SBP; systolic blood pressure, RVET/PAAT; right ventricular ejection time/pulmonary artery acceleration time ratio, PDA; patent ductus arteriosus, PFO; patent foramen ovale.

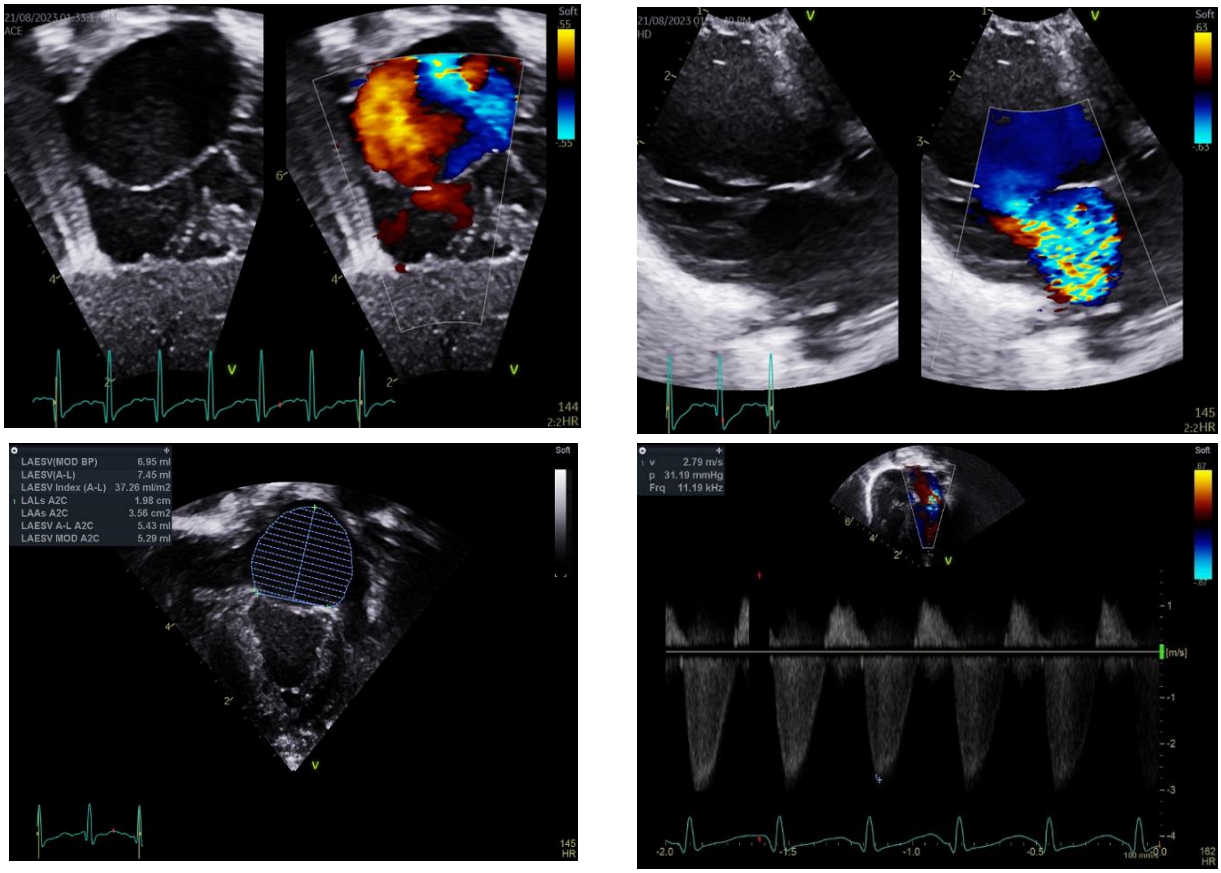

Figure 2 *(clockwise from top left corner): A) Subcostal atrial focused view demonstrating left atrial dilatation and PFO shunt. B) Mitral regurgitation jet seen on the parasternal long axis view. C) left atrial focused apical 2 chambers view. D) mitral regurgitation peak velocity seen on the apical 4 chamber view.*

Discussion

Pulmonary hypertension (PH) is a heterogeneous, cardiopulmonary clinical entity characterized by elevated mean pulmonary artery pressure (mPAP) exposing the right ventricle to high afterload[3]. Physiologically, mPAP is directly related to pulmonary blood flow (PBF), pulmonary vascular resistance (PVR) and pulmonary capillary wedge pressure (PCWP) defined by the following equation: **mPAP= (PBF x PVR) + PCWP]**[3]. In the majority of cases of PPHN, the predominant pathophysiology is elevated PVR either from maldeveloped or maladapted pulmonary vasculature (Figure 3)[4].

However, given the timing of presentation (at 24 hours of life) and presence of a dilated LA secondary to LA preload, elevated PCWP and pulmonary venous hypertension (PVH) is likely the predominant pathophysiology causing PPHN in our case. Pulmonary venous hypertension develops secondary to left-sided heart disease, from either structural causes (pulmonary venous occlusive disease, mitral/aortic valve disease or LV outflow obstruction), or functional causes (LV systolic or diastolic dysfunction). In the context of an urgent scan, LV diastolic function was not evaluated in our case, as the primary cause of MR was identified.

In a recent large cohort study, the prevalence of cardiac malformations in infants exposed to lithium in utero was estimated at 2.4%, with right-sided lesions (Ebstein's anomaly, pulmonary or tricuspid atresia) being the most common[5]. To the best of our knowledge, while mitral atresia with other left sided heart defects have been previously described in 2 infants in the literature[6], this is the first description of mitral valve dysplasia in an infant exposed to in-utero lithium.

In paediatrics and neonates, pulmonary arterial hypertension is often synonymous with PH. There is limited literature describing PVH in this population and its contribution to PPHN has been rarely described. This may, in part, be due to the diagnostic challenge of PVH in the absence of cardiac catheterization. However, few recent pilot studies have highlighted the potential role of inferior LV diastolic function and subsequent pulmonary venous congestion and edema on respiratory diseases in premature neonates[7-9].

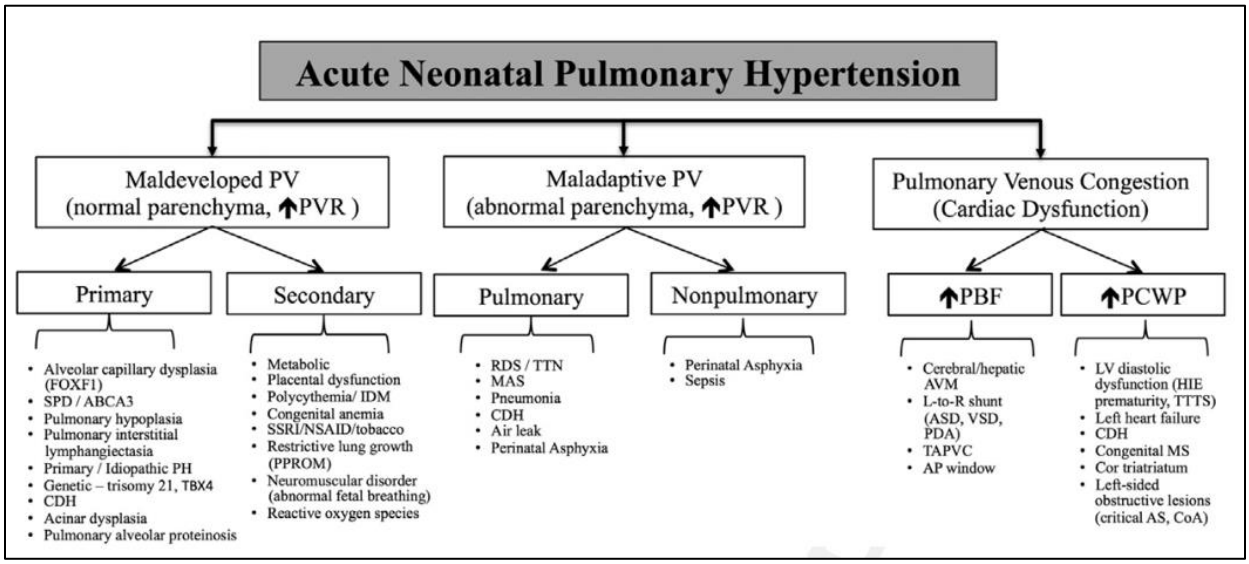

Figure 3. Pathophysiological factors associated with neonatal acute pulmonary hypertension[4].

For term infants with PPHN, the first-line use of inhaled nitric oxide (iNO) is commonly employed and has demonstrated a reduced need for extracorporeal membrane oxygenation (ECMO) and mortality[10]. However, in our case of PVH causing PPHN, the use of pulmonary vasodilators such as iNO, would potentially risk further worsening of acute pulmonary edema and respiratory compromise as it would increase the PBF; highlighting the importance of understanding the underlying physiology using TNE in acutely unwell infants to guide clinical care. Our therapeutic goals for this infant were to manage the pulmonary edema and to avoid increased LV afterload. Milrinone (inotrope, lusitrope, and systemic vasodilator used in the management of LV dysfunction) can be considered to indirectly decrease PVR and increase RV function[11]. There was no increased LV afterload in our case.

Diuretic treatment is often used in the NICU to manage symptoms of systemic or pulmonary congestion. In the context of pulmonary edema, excessive interstitial fluid, over time, can disrupt the structural integrity of the capillaries through external compression which may lead to the redistribution of pulmonary blood flow within a smaller cross-sectional area, further increasing the intra-capillary pressure[12]. In preterm

infants with chronic pulmonary hypertension, where pulmonary edema plays an important pathophysiological role, we have previously demonstrated significant improvement in TNE indices of PVR and biventricular global function within 2 weeks of diuretic therapy and a reduction in respiratory support requirements in the majority of infants after 1 week of diuretic therapy[13].

Hence, diuretics in this case was aimed at increasing the interstitial fluid reabsorption and resolution of pulmonary edema and potentially preserving LV global function to provide symptomatic relief and reduce the need for prolonged respiratory support.

Case evolution and outcome

The following day, a structural paediatric echocardiography confirmed our findings of a thickened and dysplastic mitral valve with severe MR, alongside a dysplastic tricuspid valve with moderate tricuspid regurgitation and an estimated RVSP which remained isosystemic. The LA and LV remained dilated but biventricular function was preserved. The PDA was exclusively shunting left-to-right and the PFO remained bidirectional, most likely related to the improved pulmonary edema once diuretics started. The infant continued on diuretics and was successfully weaned off CPAP within 4 days. A follow up echo prior to discharge showed improvement in pulmonary pressures with normalized interventricular septal curvature and a trivial TR jet following the closure of PDA and PFO. The infant was subsequently discharged home on diuretic therapy at 1 week of life. At her follow up appointment with paediatric cardiology at 3 weeks of age, she remained well with no interim hospital admissions required.

Conclusion:

This case highlights the importance of evaluating the pathophysiology of PPHN to guide appropriate management for these infants. Post-capillary causes of pulmonary hypertension should be considered especially in infants who are at risk of left-sided cardiac structural or functional anomalies.

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