NEONATAL HEMODYNAMICS Research Centre

Case Report

# A preterm neonate with acute pulmonary hypertension and rapidly evolving physiology

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**Key learning points:**

1. aPH is a state of dynamic physiology that can rapidly evolve and it is important to recognize that it can sometimes be secondary to a left heart phenotype causing pulmonary venous hypertension and impacting the right heart as opposed to primary pulmonary pathology.
2. Always remember the fundamentals of acute pulmonary hypertension physiology: Pulmonary arterial pressure (PaP) = (Pulmonary blood flow x pulmonary vascular resistance) + post capillary wedge pressure (Pcwp)
3. A structured, sequential approach to management including targeted neonatal echocardiography allows for optimal patient care and improves morbidity and mortality.

## Background

Acute pulmonary hypertension (aPH) is a hemodynamic state that is typically characterized by increased pulmonary artery pressure culminating in hypoxemic respiratory failure (HRF) It has many different aetiologies including pulmonary venous congestion secondary to left heart dysfunction as well as persistently elevated pulmonary vascular resistance, often due to disruption of normal post-natal transition.[1] The incidence is reported as 0.2% and 2% of live births among term and preterm neonates respectively and in some cases there may be multiple contributory processes.[1] We present a case of an extremely preterm neonate with aPH associated with biventricular cardiac dysfunction, in whom the underlying pathophysiology rapidly evolved, highlighting the importance of a structured and sequential hemodynamic approach.[2] Targeted neonatal echocardiography (TNE) is valuable to assist in the timely diagnosis of aPH, aiding in distinguishing different phenotypes of aPH, allowing for rapid reassessments and tailored management to the evolving physiological states.[2]

## Prenatal and birth history

28 week gestation neonate born to a 38 year old gravida 1 para 0 woman whose pregnancy was uncomplicated up until 26 weeks, at which time spontaneous preterm premature rupture of membranes (PPROM) occurred. Two doses of intramuscular betamethasone 24 hours apart were administered along with penicillin G and erythromycin. She was initially managed expectantly but developed preterm labour and delivered a female neonate vaginally at 28 weeks gestation.

The neonate was non-vigorous after birth with bradycardia and cyanosis. She underwent immediate cord clamping. She was started on positive pressure ventilation and was subsequently intubated by 10 minutes after birth for poor respiratory effort and low oxygen saturation ($SPO_2$) APGAR scores were 5,6,6, at 1,5,10 minutes of life respectively. Birth weight was 1.1 kg ($60^{th}$%), head circumference 26 cm ($57^{th}$%), and length 40 cm ($52^{nd}$%). Umbilical cord gases were normal. She was started on high frequency jet ventilation (HFJV) in the resuscitation room and treated with 1 dose of

intra-tracheal surfactant but subsequently developed a left sided tension pneumothorax. Needle thoracentesis was performed and 300 mLs of air was drained. A pigtail chest tube was inserted into the left pleural space (Figure 1). Following the chest tube insertion, $SpO_2$ stabilized at >90% and fraction of inspired oxygen ($FiO_2$) weaned to 0.3. A blood culture was drawn, broad spectrum antibiotics administered intravenously and she was subsequently admitted to the NICU.

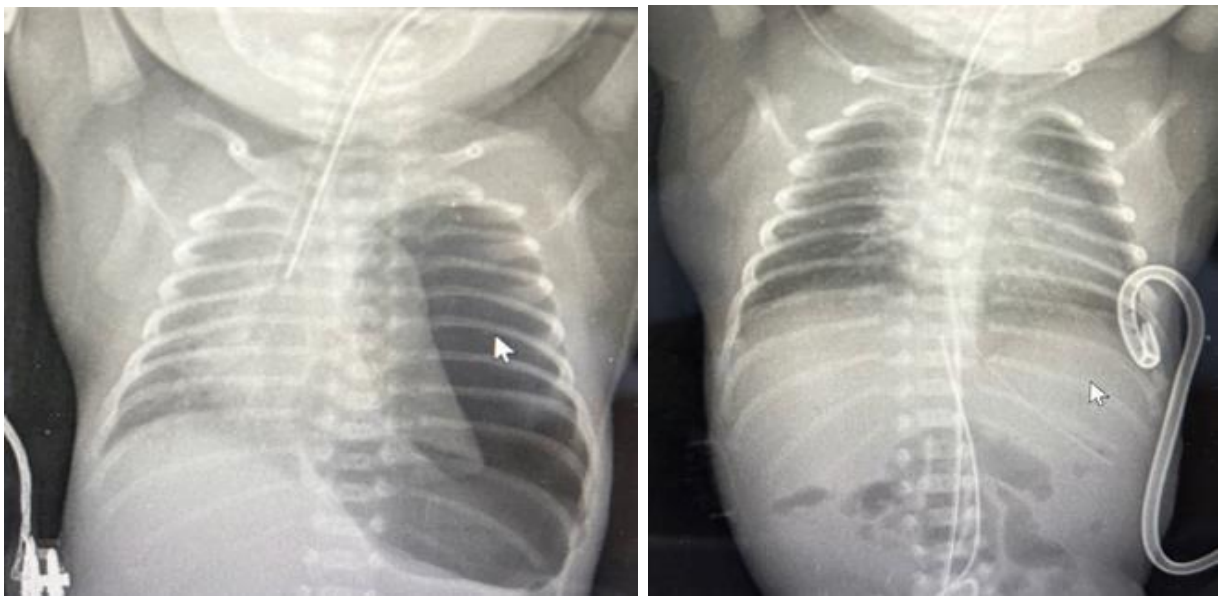

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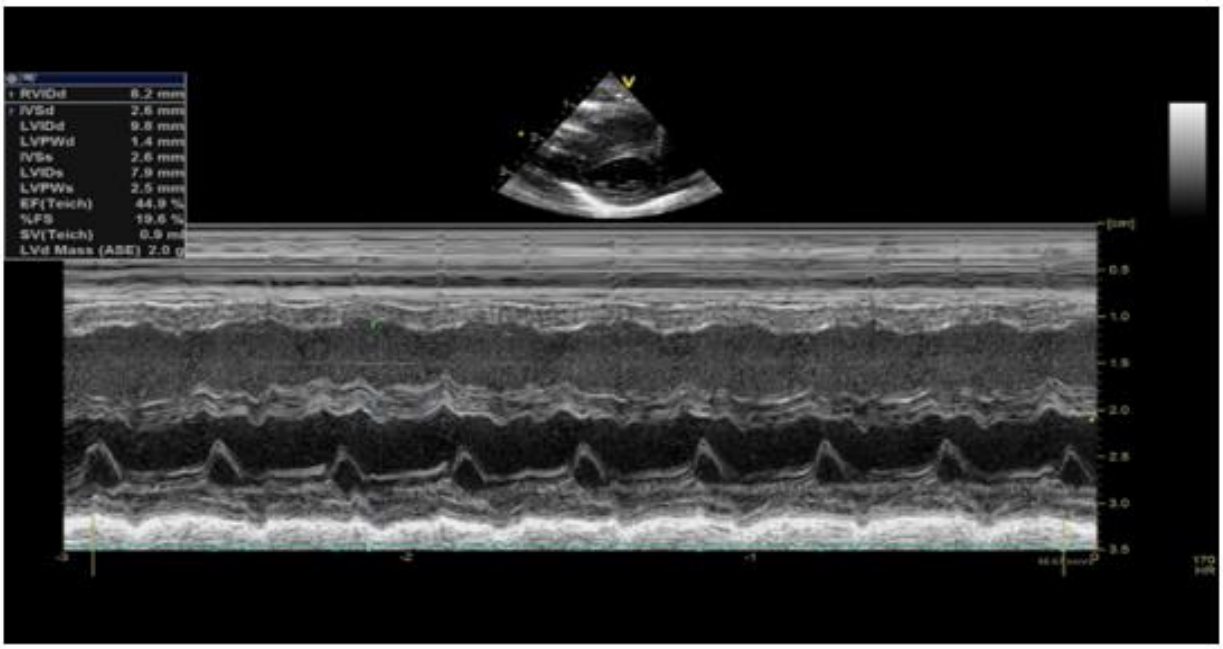
**Figure 1.** Chest radiographs demonstrating a large left-sided tension pneumothorax with mediastinal shift to the right (A) and with resolution after chest tube insertion (B).

**Clinical Scenario with Discussion**

Post admission to the NICU, the initial arterial blood gas (ABG) showed significant metabolic and lactic acidosis (likely secondary to the birth history) with pH 7.1 $pCO_2$ 56 mmHg, $PaO_2$ 28 mmHg, bicarbonate 17 mmol/L, base deficit -14 (7.1/56/28/17/-14) lactate 11mmol/L. The complete blood count revealed hemoglobin 168g/L, total white blood cell count 25.5 x $10^9$/L and platelet count 296 x $10^9$/L.

A neonatal hemodynamics/TNE (NHTNE) consultation was requested and performed at 4 hours of age due to the development of systolic (SAP) hypotension with narrow pulse pressures and worsening hypoxemic respiratory failure requiring $FiO_2$ 1.0. At the time of assessment, her heart rate was 166 bpm, axillary temperature 36.6 degrees Celsius, blood pressure 35/31 mmHg (via indwelling umbilical arterial catheter) and $SPO_2$ 83% pre- and 72% post-ductal. Her ventilatory pressures were: peak inspiratory pressure (PIP) 30 $cmH_2O$, positive end expiratory pressure (PEEP) 9 $cmH_2O$, mean airway pressure (MAP) 12 mmHg, inspiratory time (Ti) 0.02 seconds, rate 300 per minute, and $FiO_2$ 1.0. Her ABG showed 7.21/61/29/20/-5. She was sedated with an intravenous infusion of fentanyl 1mcg/kg/hour, muscle relaxed with an intravenous dose of rocuronium (0.6 mg/kg). She was also empirically started on an intravenous infusion of epinephrine 0.05 mcg/kg/min by the primary care team prior to the TNE consultation. Initial TNE findings are shown below in figure 2 and table 1:

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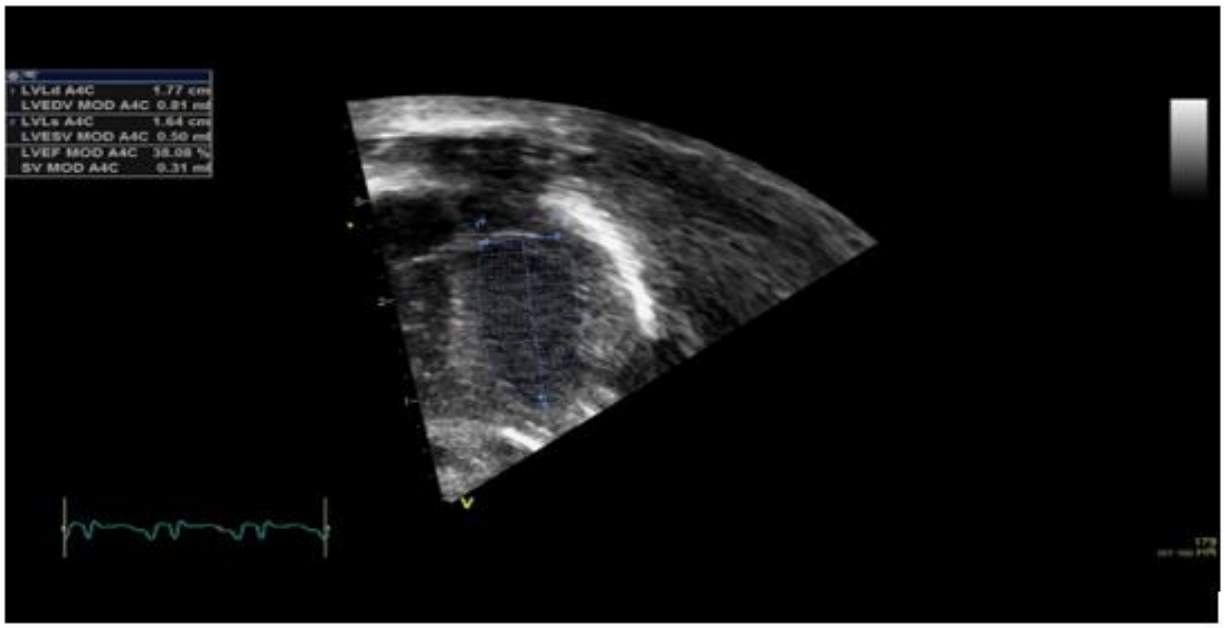


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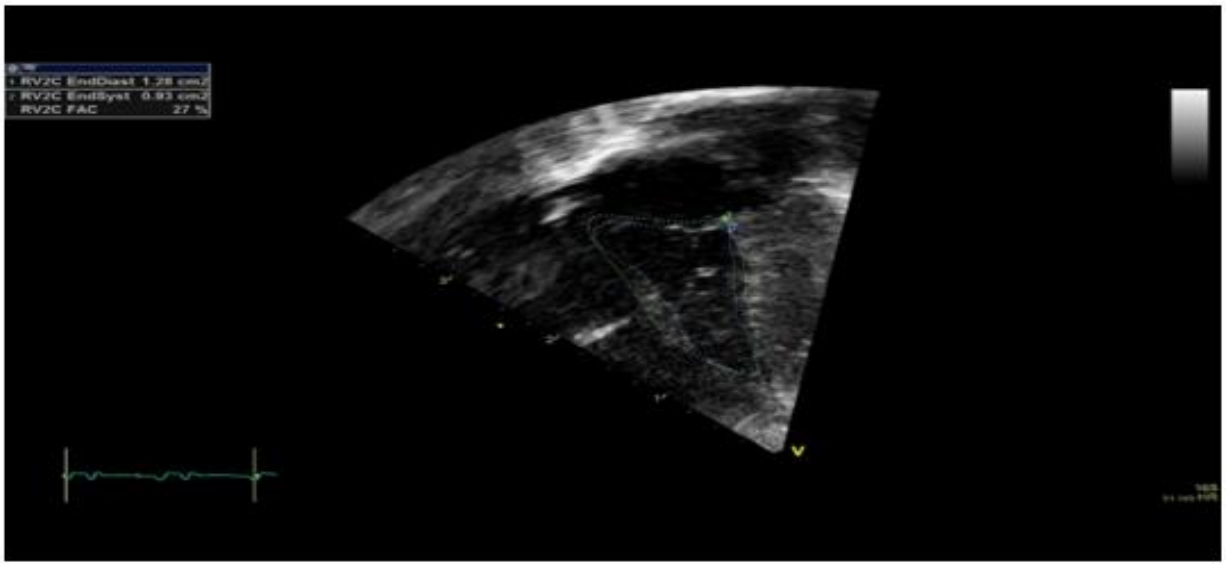


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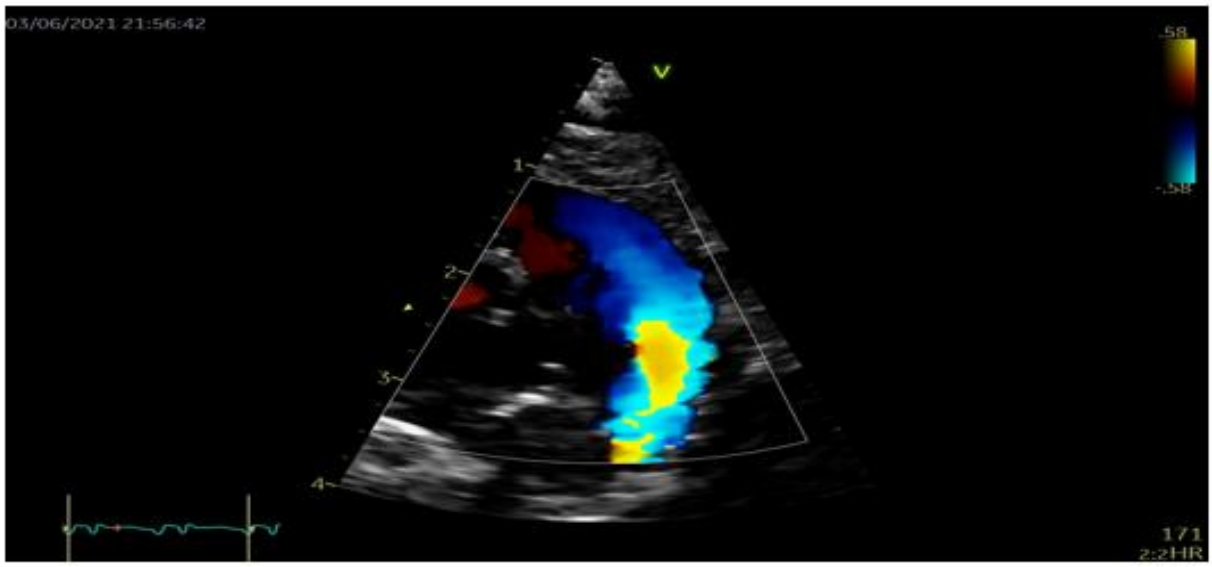


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**Figure 2.** Initial TNE- (A) M-Mode showing reduced Fractional shortening (FS) and Ejection fraction (EF) % (B) Left ventricle (LV) focused apical view showing decreased Simpson's biplane (C) Right ventricle (RV) focused apical view showing reduced fractional area change (FAC) 27% (D) Ductal view with large patent ductus arteriosus (PDA) shunting R-L shunt

| Table 1- Initial TNE Findings | |
|---|---|
| **Echo parameter** | **Findings** |
| LV function | EF biplane 40%, EF M-mode 45%<br>FS 19.6%<br>LVO 91 ml/kg/min *(Normal = 150-200ml/kg/min)* |
| RV function | TAPSE 4.2 mm<br>RV2C FAC 27% , RV3C FAC 40%<br>RVO 165 ml/kg/min *(Normal= 150-200ml/kg/min)* |
| PDA | Diameter 4.3mm<br>Shunt : R-L (unrestrictive)<br>PA:Ao ratio: Max PG 2.5mmHg; Mean PG 1.3 mmHg |
| Pulmonary pressures | TR PG (max) 44.3mmHg<br>IVS curvature- Flat in systole+ diastole<br>PDA R-L<br>PASp suprasystemic from PDA shunt direction |
| PFO | Diameter 2.8 mm<br>Shunt direction – mostly R-L |
| Other | Situs solitus, levocardia, atrio-ventricular and ventriculo-arterial concordance. Normal cardiac valves, normal systemic and pulmonary venous drainage and no ventricular inflow or outflow obstruction. Unobstructed left sided aortic arch. |

*(**Key-** Ao:PA – Aortic to pulmonary, EF –ejection fraction, FAC- fractional are change, FS- fractional shortening, IVS- Intraventricular septum, LV- left ventricle, LVO-left ventricular output, PASp- pulmonary artery systolic pressure, PDA- patent ductus arteriosus,, PFO-patent foramen ovale , PG – pressure gradient, RV–right ventricle, RV2C – right ventricle 2 chamber, RV3C – right ventricle 3 chamber, RVO- right ventricular output, TAPSE- tricuspid annular plane systolic excursion, TR- tricuspid regurgitation, Vmax- maximum velocity)*

The findings of the TNE showed a pattern of aPH with mixed aetiology (elevated pulmonary venous pressure and pulmonary disease). This physiological state was probably due to the combination of acute hypoxic ischemic injury from the large tension pneumothorax causing obstructive shock, with ongoing sequela despite resolution of the pneumothorax with chest tube placement. . This likely resulted in pathological hypoxia impairing myocardial performance and promoting failure of pulmonary vasorelaxation.

Many, but not all, of the clinical, laboratory and echocardiography findings support a diagnosis of aPH due to elevated pulmonary venous pressure. It is important when assessing cardiopulmonary hemodynamics to establish whether it is primary RV disease, LV disease, or biventricular disease but this can be difficult to delineate. The echocardiographic markers supporting the LV phenotype with pulmonary venous hypertension include the severely reduced LV systolic function, moderately reduced LVO and R to L shunt across the ductus arteriosus which are in keeping with a scenario

where the RV output supports the systemic circulation, especially in the context of only mildly reduced RV systolic function and normal RVO.

However, other elements are not completely in keeping with LV systolic dysfunction being the primary hemodynamic derangement. For example, the mostly R to L shunt across the foramen ovale suggests that the right ventricular end diastolic pressure (RVEDP) ≥ left ventricular end diastolic pressure (LVEDP), implicating a potentially important contribution of RV systolic dysfunction and high PVR.[3]

A potentially alternative explanation could be the acute effect of the epinephrine infusion that was commenced 2 hours prior to the scan on LV performance. The TNE, which is a point-in-time assessment, may have captured an improving LV systolic function due to the inotropic effect of the low-dose epinephrine whereby LVEDP was on the decline, thus potentially resulting in the heterogeneity of the echocardiography findings. One potential explanation is the effect of low dose epinephrine on peripheral B2 receptors causing a reduction in the systemic vascular resistance which may have impacted the loading conditions of the LV and then the LA compliance but inotropic effect was not yet appreciated.

LV failure in the setting of aPH should be managed in a step wise approach, especially in the context of poor LV output and potentially ductal dependent systemic circulation.[4,5]

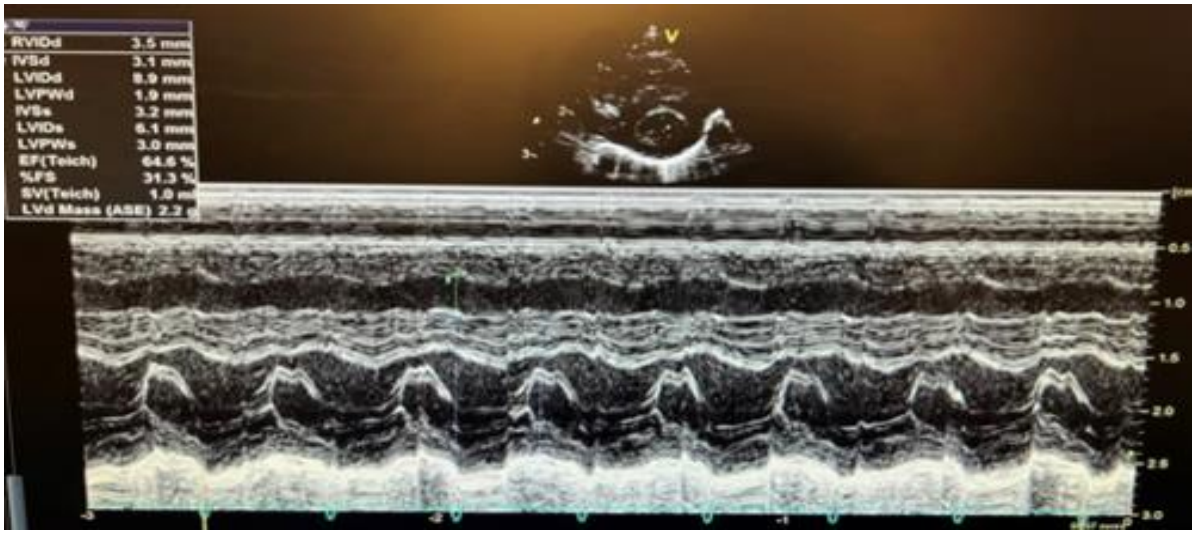
The goals of treatment in such patients would be to improve LV systolic performance and LVO as well as reducing PVR and RV afterload but avoiding abruptly reducing or reversing the R-L shunt across the PDA. Agents such as epinephrine (at lower doses of 0.03- 0.05 mcg/kg/min, maximum dose 0.2mcg/kg/min) and dobutamine (5-10mcg/kg/min) aim to improve ventricular performance through their effect on β1 cardiac receptors (positive inotropy and chronotropy) and β2 peripheral receptors (decreasing LV afterload). Medications that increase SVR and LV afterload such as norepinephrine or vasopressin should be avoided when managing aPH secondary to primary LV disase until LV systolic performance improves as increasing systemic blood pressure in the absence of inotropic support will increase LV afterload, reduce stroke volume and output and culminate in worse dysfunction.[4]

In addition, lower dosing of iNO (5ppm) can theoretically reduce PVR and RV afterload but not to an extent to severely compromise the R-L shunt across the PDA.[6] Higher concentrations of iNO and oxygen may be detrimental as they could decrease PVR and lead to increased pulmonary blood flow at the expense of systemic blood flow.[5] Also, in the context of severe LV failure causing pulmonary venous hypertension, agents that decrease intrapulmonary vascular resistance can lead to significant pulmonary congestion and edema with subsequently hypoxic respiratory failure and rapid clinical deterioration.

**Case Evolution (1)**

The initial recommendations from the initial NHTNE consult suggested increasing the epinephrine infusion to 0.1 mcg/kg/min, adding dobutamine at 10 mcg/kg/min as well as starting low dose iNO at 5ppm. Over the next 6 hours post these recommendations, the patient remained intubated on HFJV 29/9 Rate 300, Ti 0.02, MAP 11.5. Clinically, the $FiO_2$ decreased to 0.29 and her vital signs were stable. The blood gases and lactate also improved (7.35/28/71/15/-9, lactate 3.4 mmol/L).

However, in the subsequent hours, there was worsening of the lactic acidosis with the blood gas showing 7.26/34/70/15/-11 and lactate of 6.8 mmol/L. The BP remained normal and $SPO_2$ remained >90% pre and post ductally. The next NHTNE consultation was done at approximately 12 hours after the first and at the time of the assessment, the patient was on HFJV 28/9 $FiO_2$ 0.29, $SPO_2$ 98% pre + 89% post, HR 166, BP 40/34. Prior to the NHTNE assessment, the primary care team empirically increased the iNO to 10 ppm, started vasopressin at 1.2 mU/kg/min, increased epinephrine to 0.2mcg/kg/min and dobutamine to 20 mcg/kg/min for presumed deteriorating clinical status. The TNE findings are shown in figure 3 and table 2:

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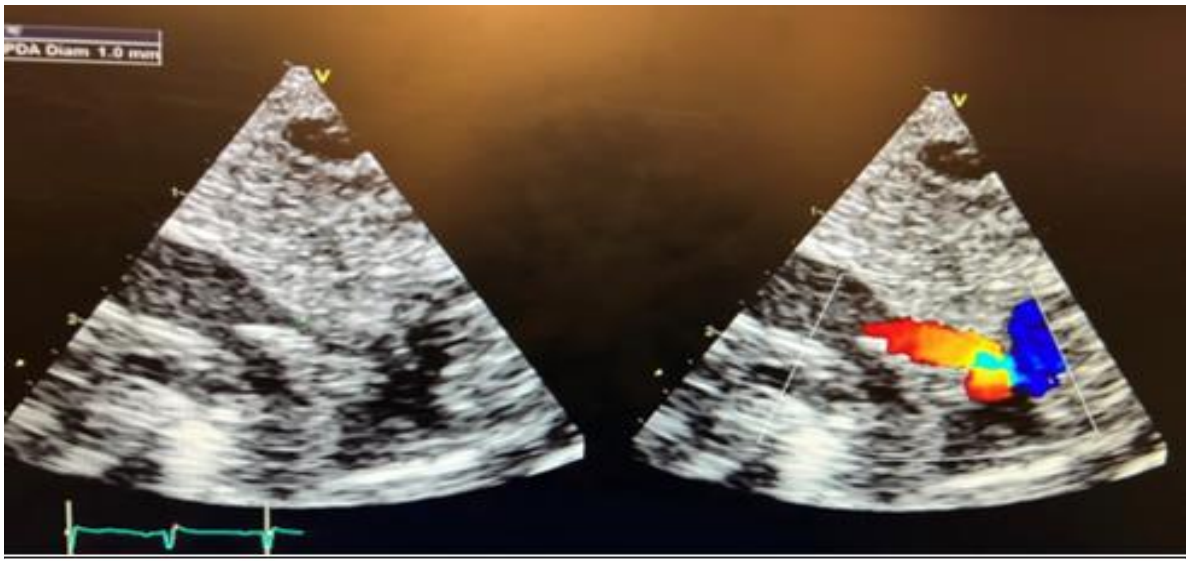


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**Figure 3. Second TNE- (A)** M-mode showing improved FS+EF **(B)** Ductal view showing small, restrictive PDA with bi-directional shunt

| Table 2- Second TNE Findings | |
|---|---|
| **Echo parameter** | **Findings** |
| LV function | EF biplane 69.6%, EF M-mode 64.6%<br>FS 31.3%<br>LVO 94 ml/kg/min<br>Qualitatively under-filled, hyperdynamic |
| RV function | TAPSE 2.3 mm<br>RV2C FAC 25% , RV3C FAC 35%<br>RVO 95 ml/kg/min |
| PDA | Diameter 1.0 mm<br>Shunt: restrictive, bidirectional |
| Pulmonary pressures | TR Vmax 11.5 mmHg<br>IVS curvature- Flat in systole+ diastole<br>PDA bidirectional<br>PASp near systemic (Ao-PA gradient 4.1mmHG; mean 1.8mmHg) |
| PFO | Diameter 2.5 mm<br>Shunt direction – bidirectional |

The most logical explanation with the sequence of events between TNE assessments is as follows: *1st TNE showing LV + RV dysfunction + aPH -> addition of inotropic support-> improvement of LV function -> ongoing aPH + high PVR and RV afterload-> worsening RV dysfunction + decreased LVO (decreased LV preload + increased LV afterload).* This can also be inferred and linked with the trend in the blood gases and lactates which showed initial improvement then deteriorated as the physiology shifted.

The TNE showed improved LV systolic function on biplane and m-mode but persistently low LVO. There was worsening of the RV systolic function and output with minimal improvement in the pulmonary hypertension. The PDA was smaller in caliber 1.0 mm with a bidirectional shunt indicating PASp was still at almost systemic level.

Clinically, the patient was no longer in HRF (as manifested by the normal BP and SPO2 >90%) but had worsening of metabolic/lactic acidosis. This could be explained by the fact that there was improvement in the LV systolic performance likely due to the positive effect of the inotropic medications but the LVO remained low because of under-filling of the LV (potentiated by tachycardia secondary to the chronotropic effects of epinephrine and dobutamine) coupled with an increased afterload from the effect of vasopressin on the SVR. The RV systolic function and RVO deteriorated due to the ongoing high afterload from the pulmonary hypertension and represents the more traditional physiologic phenotype.

Considering the formula for Delivery of oxygen ($DO_2$) to tissues:
$DO_2 = [(1.34 \times Hgb \times SpO_2/100) + (0.003 \times PaO_2)] \times$ Cardiac output * local perfusion pressure, the worsening lactic acidosis could likely be caused by anaerobic metabolism due to decreased $DO_2$ primarily from poor cardiac (ventricular/LVO) output, especially considering the improved SpO2, normal BP (perfusion pressure), normal Hgb and $PaO_2$.

The goal of managing patients in this clinical situation should be to improve both ventricular outputs thus improving pulmonary (Qp) and systemic blood flow (Qs). RVO would be improved by reducing the PVR and afterload on the RV by utilizing agents such as iNO and liberal oxygen as first line management to achieve effective pulmonary vasorelaxation.[7] RVO can also be augmented by inotropic medications to improve contractility and increasing preload.

It is important to remember that the effect of iNO on PVR could be rapid, leading to a greatly increased Qp:Qs ratio (especially in the context of a PDA) and consequently pulmonary over-circulation, pulmonary edema and decreased systemic perfusion (systemic steal).[8,9]

Strategies to improve the LVO in the context of normal contractility would be to improve the preload by giving extra fluid volume to improve LV filling, decreasing heart rate (force frequency mechanism), and decreasing the afterload (Frank-Starling mechanism).

**Case Evolution and Outcome**

A third TNE was done 4 hours after the second study. The neonate was clinically stable with normal BP (41/31 mmHg) and her FiO2 was able to be weaned to 0.21. Her blood gases and lactate also showed improvement (7.29/43/52/20/-6; lactate 3.2 mmol/L)

The TNE showed normal LV systolic function with improved LVO (EF biplane 66.4%, EF M-mode 65.4%, FS 32%, 150 ml/kg/min). The RV systolic function and RVO was also improved (TAPSE 3.7mm, RV2C FAC 27%, RV3C FAC 35%, 163 ml/kg/min). The pulmonary hypertension was also improved (IVS flat, mild TR – max PG 25 mmHg, PASp now 2/3 systemic level from PDA Doppler). The PFO was mostly L-R and the PDA still small with restrictive L-R shunt.

She was followed with serial echoes until normalization of function and pulmonary pressures as well as frequent blood gases and lactate measurements as markers of reduced peripheral perfusion. Inotropic support was weaned off by 5 of life. Muscle relaxation was stopped on day 5 and sedation was eventually weaned off by day 21. The iNO was weaned off by day 7 and the chest tube was also removed on day 7. She was extubated to CPAP by day 9 and was eventually weaned to room air by 2 months of age. Any metabolic or hematological derangements were corrected. Amplitude integrated EEG was initially placed post admission, but tracing was normal so stopped on day 2. Multiple sepsis screens were performed, beginning from birth, however all tests were negative for infection. Enteral feeding was started on day 7 and full feeds established by day 16. She was eventually transferred to a level 2 unit at a corrected gestational age of 38 weeks for ongoing management.

**Conclusion**

This case highlights the dynamic pathophysiology associated with acute pulmonary hypertension and the need for a multidisciplinary structured and sequential approach to management. Our strategy demonstrates the importance of NHTNE and the ability to make adjustments in real time to improve the outcome of patients affected by this illness.

**References**

1. Sankaran D, Lakshminrusimha S. Pulmonary hypertension in the newborn- etiology and pathogenesis. Semin Fetal Neonatal Med. 2022 Aug;27(4):101381. doi: 10.1016/j.siny.2022.101381. Epub 2022 Aug 7. PMID: 35963740.

2. de Boode WP, Singh Y, Molnar Z, Schubert U, Savoia M, Sehgal A, Levy PT, McNamara PJ, El-Khuffash A; European Special Interest Group 'Neonatologist Performed Echocardiography' (NPE). Application of Neonatologist Performed Echocardiography in the assessment and management of persistent pulmonary hypertension of the newborn. Pediatr Res. 2018 Jul;84(Suppl 1):68-77. doi: 10.1038/s41390-018-0082-0. PMID: 30072805; PMCID: PMC6257221.

3. Ruoss JL, Moronta SC, Bazacliu C, Giesinger RE, McNamara PJ. Management of cardiac dysfunction in neonates with pulmonary hypertension and the role of the ductus arteriosus. Semin Fetal Neonatal Med. 2022 Aug;27(4):101368. doi: 10.1016/j.siny.2022.101368. Epub 2022 Jun 11. PMID: 35798649.

4. Abdel Massih AF, Al Zahraa Hassan F, El-Gammal A, Tawfik M, Nabil D. The overlooked left ventricle in persistent pulmonary hypertension of the newborn. J Matern Fetal Neonatal Med. 2021 Jan;34(1):72-76. doi: 10.1080/14767058.2019.1598363. Epub 2019 Mar 28. PMID: 30895828.

5. McNamara PJ, Giesinger RE, Lakshminrusimha S. Dopamine and Neonatal Pulmonary Hypertension-Pressing Need for a Better Pressor? J Pediatr. 2022 Jul;246:242-250. doi: 10.1016/j.jpeds.2022.03.022. Epub 2022 Mar 18. PMID: 35314154.

6. Finer NN, Sun JW, Rich W, Knodel E, Barrington KJ. Randomized, prospective study of low-dose versus high-dose inhaled nitric oxide in the neonate with hypoxic respiratory failure. Pediatrics. 2001 Oct;108(4):949-955. DOI: 10.1542/peds.108.4.949. PMID: 11581449.

7. Cookson MW, Abman SH, Kinsella JP, Mandell EW. Pulmonary vasodilator strategies in neonates with acute hypoxemic respiratory failure and pulmonary hypertension. Semin Fetal Neonatal Med. 2022 Aug;27(4):101367. doi: 10.1016/j.siny.2022.101367. Epub 2022 Jun 3. PMID: 35688685.

8. Bischoff AR, Giesinger RE, Neary E, Weisz DE, Belik J, McNamara PJ. Clinical and echocardiography predictors of response to inhaled nitric oxide in hypoxemic term and near-term neonates. Pediatr Pulmonol. 2021 May;56(5):982-991. doi: 10.1002/ppul.25252. Epub 2021 Jan 12. PMID: 33434418.

9. More K, Soni R, Gupta S. The role of bedside functional echocardiography in the assessment and management of pulmonary hypertension. Semin Fetal Neonatal Med. 2022 Aug;27(4):101366. doi: 10.1016/j.siny.2022.101366. Epub 2022 Jun 14. PMID: 35718687.