NEONATAL HEMODYNAMICS Research Centre

Case Report

Hemodynamic effects of prostaglandin infusion in refractory severe persistent pulmonary hypertension of the newborn associated with congenital CMV infection

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Key physiological insight/learning points:

PPHN refractory to pulmonary vasodilators may result in progressive RV dysfunction and LV compromise through adverse ventricular-ventricular interactions.

Sequential TNE evaluations allow prompt hemodynamic phenotyping at the bedside, supporting timely institution of precise treatment.

Pharmacologic re-opening of ductus arteriosus may result in acute reversal of RV dilatation and failure and allow hemodynamic stabilization in refractory PPHN.

Sequential monitoring of natriuretic peptides may aid longitudinal monitoring of disease progression/resolution after initial phenotyping with TNE.

Background: Persistent pulmonary hypertension of the newborn (PPHN) may arise secondary to a wide range of diseases, and is a significant contributor to neonatal morbidity and mortality [1,2]. While inhaled nitric oxide (iNO) is considered the treatment of choice for PPHN, approximately 40% of patients are iNO resistant, prompting the need for additional therapies [3]. When resistant to treatment, PPHN may result in right ventricular (RV) dysfunction, which may worsen prognosis [4]. Here we present a case of a late preterm infant with congenital cytomegalovirus (CMV) infection, who presented with severe refractory PPHN and RV failure which responded to pharmacological opening of the ductus arteriosus (DA). We highlight the importance of close monitoring with sequential targeted neonatal echocardiography (TNE) and hemodynamic effects of prostaglandin infusion for refractory PPHN.

BW & Birth GA:

This is the case of a preterm infant born at 36 1/7 weeks of gestational age and a birth weight of 2145 grams.

Birth History and initial resuscitation:

The pregnancy was complicated by acute CMV infection with positive maternal CMV IgM and CMV PCR of the amniotic fluid. The fetal MRI demonstrated bilateral periventricular deep white matter foci compatible with calcification or hemosiderin, as well as bilateral periventricular cysts and prominent temporal white matter. Spontaneous onset of labor occurred at 36 weeks gestational age with rupture of membranes ~3 hours prior to delivery. The baby was born via spontaneous vaginal delivery and had adequate respiratory effort, normal heart rate and tone. Apgar scores were 9 and 8 at one and five minutes, respectively. The cord gases were normal. The infant initially required free flowing oxygen to maintain saturations within target range and was later transitioned to nasal continuous positive airway pressure (nCPAP) 5 cmH2O, needing 25% oxygen.

Medical History:

The baby remained stable from a cardiorespiratory perspective during the initial

phase and was weaned to low flow oxygen on DOL 2. Urine CMV PCR was positive, and plasma viral load was 3.28 X 10^6 IU/mL, confirming the diagnosis of active infection with CMV. Head ultrasonography demonstrated bilateral periventricular calcifications and laboratory tests confirmed hepatitis (ALT 160 unit/L) and thrombocytopenia (Platelet count 12 X 10^9/L). Infant was commenced on intravenous therapy with ganciclovir on DOL 3. On DOL 5, infant developed increased work of breathing, oxygenation difficulties requiring escalation of oxygen needs to 50%, and acute metabolic acidosis. The respiratory support was escalated gradually from low flow oxygen to nasal intermittent positive pressure ventilation (NIPPV) and mean airway pressure was increase to 12 cmH2O to allow adequate recruitment, confirmed by a chest radiography which demonstrated normal lung aeration with mild cardiomegaly. A structural echocardiographic assessment was completed, which ruled out structural abnormality but was reported to show suprasystemic pulmonary pressures and qualitative RV dysfunction and dilation. These findings prompted an urgent request for consultation through the in-patient TNE and neonatal hemodynamic service.

Hemodynamic Consultation:

The initial hemodynamic assessment confirmed severe pulmonary hypertension with right ventricular peak systolic pressure (RVSP) of 80 mmHg, gross RV dilatation and systolic dysfunction with a tricuspid annular plane systolic excursion (TAPSE) of 5 mm, as well as low right ventricular output (RVO) of 86 ml/min/kg. Additionally, mildly reduced left ventricular (LV) systolic function (Simpson's biplane 31%) as well as absence of shunt through the DA were also noted. Following conversations with the attending team, baby was started on 20 parts per million of iNO non-invasively. In view of the significant RV dysfunction and low RVO in the presence of robust systemic blood pressure (88/66), intravenous milrinone infusion was also initiated with an initial loading dose of 25 mcg/kg followed by maintenance of 0.33 mcg/kg/min. Laboratory cardiac markers were evaluated which showed a high level of N-terminal pro b-type natriuretic peptide (NT-proBNP) of >4000 pmol/L and Troponin-T (270 ng/L). A TNE performed 6 hours after demonstrated some improvement in RVO to 112 ml/min/kg, and TAPSE of 6 mm. However, there was no change in severity of PPHN and RV dilatation.

Over the next 48 hours the baby was invasively ventilated, sedated and muscle relaxed on account of severe hypoxemic respiratory failure requiring 100% oxygen. During this time, several pulmonary vasodilators were added along with sequential TNE assessments and laboratory investigations to ensure close monitoring. These included optimizing dosage of intravenous milrinone to 0.99 mcg/kg/min, intravenous sildenafil to 1.5 mg/kg/day as well as magnesium sulfate up to 35 mg/kg/hour. While these therapies were well tolerated and were associated with normalization of cardiac outputs and improvement in RV systolic function on TNE (TAPSE increased to 7.6 mm), the RVSP remained high (73 mmHg). More concerning finding was the further progression of RV dilatation and reduction in LV size manifested by worsening ratio of RV to LV end diastolic area (from 1.53 in the initial echo to 1.71), suggesting compromised LV filling on account of adverse V-V interaction **(Figure 1, Panel A and B)**. Clinically, infant continued to require 100% oxygen and NT-proBNP levels remained >4000 pmol/L. At this point, given the refractory nature of pulmonary hypertension and hypoxemia, with the intention to offload the right ventricle and prevent LV failure, intravenous prostaglandin infusion (alprostadil) was commenced at 0.1 mcg/kg/min. The infant demonstrated significantly higher pre-ductal saturations than post-ductal soon after, representing right to left shunt across the DA, confirming efficacy of treatment to re-open the DA.

This DA re-opening was associated with significant and immediate improvement in clinical, laboratory as well as TNE findings. Over the next 24 hours the oxygen requirement improved to 60% and NT-proBNP levels came down to 2930 pmol/L **(Figure 2)**. Repeat TNE evaluation completed 16 hours after starting alprostadil infusion confirmed a moderate sized DA shunting mostly right to left and a marked qualitative and quantitative improvement in RV dilatation **(Figure 1, Panel C and D)**. This coincided with improved RV systolic function and lowering of eccentricity index from 1.77 to 1.36 **(Table 1)**.

The clinical and echocardiographic improvement allowed for and persisted despite weaning off iNO, milrinone and magnesium sulfate infusions over the next two days. A follow up TNE on DOL 10 demonstrated only mild RV dilatation, good biventricular systolic function (fractional area change of 43% and Simpson's biplane of 47%), RVSP of 39 mmHg, normal LV cavity size and a DA shunting mostly left to right. Attempt was made to discontinue sildenafil infusion, but that resulted in an increase in NT-proBNP levels as well as RVSP and RV size confirmed on TNE. These resolved after restarting sildenafil. Infant was maintained on alprostadil infusion and sildenafil for the next 2 weeks. During this time, the oxygen requirements improved to 26-30%, NT-proBNP levels came down to 770 pmol/L and the DA became exclusively left to right. Alprostadil infusion was then discontinued on DOL 24, infant was successfully extubated to NIPPV on DOL 28 and gradually weaned and transitioned to low flow oxygen. Sildenafil was also switched to oral administration on DOL 32 for long-term treatment in collaboration and consultation with regional pediatric cardiology service. Infant's remaining stay in our NICU was unremarkable. However, despite optimal treatment with IV ganciclovir, the viral load remained very high – up to 6.91 X 10^6 IU/mL, warranting ongoing inpatient care. On DOL 56, given the hemodynamic stability and family's wishes, infant was transferred to a community level 2 unit with local pediatric cardiology follow up.

Discussion

PPHN is described as hypoxemia secondary to failure of adequate drop in pulmonary vascular resistance following birth. It is a common entity encountered in the NICU, which can originate from a wide variety of causes [1,2]. Congenital CMV has been reported as a rare culprit of the disease [5,6]. The pathophysiology of PPHN in the context of congenital CMV is thought to be secondary to vasculitis [6], and pneumonitis which has been reported to occur in approximately 6% of cases [7]. Regarding treatment of PPHN in neonates, in addition to specific treatment of the underlying disease, iNO is the only proven and approved pulmonary vasodilator in term and near-term neonates. However, significant proportion of patients do not improve despite iNO treatment, and need a more physiology-based approach to evaluation and treatment [8]. Resistance to iNO may be secondary to inadequate administration such as in cases of under recruited lungs, a significant parenchymal disease resulting in excessive inflammation, a chronic state causing a fixed rise in PVR which may not be vasoreactive, the need to address alternate cellular pathways, and underlying cardiac dysfunction, resulting in low pulmonary blood flow (PBF).

In infants who are iNO unresponsive, further investigation to determine the specific underlying hemodynamic phenotype is warranted [4]. These may include presence/adequacy of intra- and extra-cardiac shunts, occurrence of low PBF and systemic blood flow, and associated RV and/or LV dysfunction. Delineation of specific underlying hemodynamic phenotype is clinically challenging in neonates, as the primary symptoms are defined by severe hypoxic respiratory failure, irrespective. A comprehensive TNE, when utilized by experienced operators, can prove to be a valuable bedside tool to establish specific derangements and guide specific treatments.

Currently, there is no robust evidence to guide pulmonary vasodilatory therapies in neonates who are unresponsive to iNO, needing clinicians to use basic physiological principles and sequential close monitoring, along with local experience. In our case, we chose to use milrinone as the second line agent to target theoretically complementary cyclic AMP pathway as well as support RV dysfunction. Subsequently, on account of refractory nature of pulmonary vascular disease, sildenafil (proven in small studies to have synergistic effects with iNO and can be transitioned to oral long-term therapy if needed) and magnesium sulphate (shown in small trial to be as effective as iNO for PPHN). While we observed improvements in RV output and systolic function, despite combined pharmacotherapy, we observed no acute effect on pulmonary pressures, either clinically or on echocardiography. The main known acute side effects of systemic pulmonary vasodilator therapies that should be monitored for, are systemic vasodilation (resultant hypotension), and potential worsening in ventricular-perfusion mismatch (resultant hypoxemia, secondary to vasodilation around non-ventilated alveoli).

RV dysfunction and dilatation are a well-known upstream sequela of pulmonary hypertension. When the inherent ability of the right ventricle to compensate for the high afterload by increasing contractility is saturated, ventriculo-arterial uncoupling occurs and ventricle failure ensues. RV failure may lead to low RV output, thus contributing to the hypoxemic respiratory failure by virtue of a low PBF state. LV dysfunction may also be present in PPHN and be explained by several potential mechanisms: (i) Reduced LV preload secondary to RV dysfunction and low PBF, (ii) Adverse ventricular–ventricular interactions owing to shared myocardial fibers [9,10], or (iii) Secondary to dilatation of the RV occurring at the expense of the LV due to pericardial restrain, as was apparent in the presented case. While RV dilatation is an adaptive mechanism to maintain cardiac output in the face of high afterload, through Frank Starling effect (increase in end-diastolic volume results an increase in ventricular output), it comes at the expense of increase in wall stress and associated myocardial work [wall stress (= afterload felt by the myocardial wall) is directly related to the radius of curvature of ventricular wall, which increases with dilation). Further, beyond a certain point, the Frank Starling curve plateaus, such that further increase in end-diastolic volume does not result in improvement in cardiac output but continue to raise the wall stress. Patients with RV dilatation, particularly from acute pulmonary hypertension, must be closely monitored progression to dysfunction (fatigued right ventricle) may have catastrophic and irreversible consequences.

Pharmacologic opening of the DA in this scenario has been well described in the literature [11,12]. Physiologically, a patent DA in the context of RV failure due to suprasystemic pulmonary pressures would enable the right ventricle to offload to the systemic circulation, thus reducing the afterload and reinstating ventriculo-arterial coupling. In this case, the opening of the DA significantly and acutely improved RV dilatation and dysfunction, allowed the patient to be stabilized and resulted in marked and persistent improvement in oxygenation. Further, prostaglandins, through their effect on the cAMP pathway, may also promote pulmonary vasodilation, an additional benefit in acute pulmonary hypertension. In our case, at least acutely, we did not see any improvement in pulmonary pressures as evident by a right to left shunt at the ductal level. This suggested that the acute improvement in oxygenation was mostly in association with its effect of offloading the pressure-loaded right ventricle. However, subsequent improvement in pulmonary pressures over a period, which allowed us to wean off other unresponsive vasodilator therapies, may have been facilitated by the prostaglandin's vasodilatory action on pulmonary vascular bed.

Patients with refractory PPHN can present a substantial challenge to the clinical team. As the disease course progresses and additional agents are being introduced, the pathophysiology may change, thus sequential bedside TNE monitoring can be highly beneficial, as was demonstrated in this case. However, since TNE assessments are resource intensive, once the pathophysiology is established and the patient has been stabilized, sequential values of cardiac biomarkers such as NT-proBNP may also be effective in facilitating longitudinal monitoring of disease progression or response to treatments. In our case, NT-proBNP levels assisted in flagging the rebound in pulmonary pressures and RV dilatation following attempts to discontinue sildenafil treatments, which prompted a TNE evaluation to confirm and provided clinical evidence of need for long-term treatment.

In conclusion, CMV associated lung involvement causing PPHN is a rare manifestation of congenital CMV. This case highlights the complexities in the management of severe PPHN with RV dysfunction, particularly in context of lack of adequate response to iNO. In severe cases of refractory PPHN with RV failure, re-opening DA with prostaglandin infusion can be a life-saving strategy which may reverse RV dysfunction and dilatation and allow for patient stabilization.

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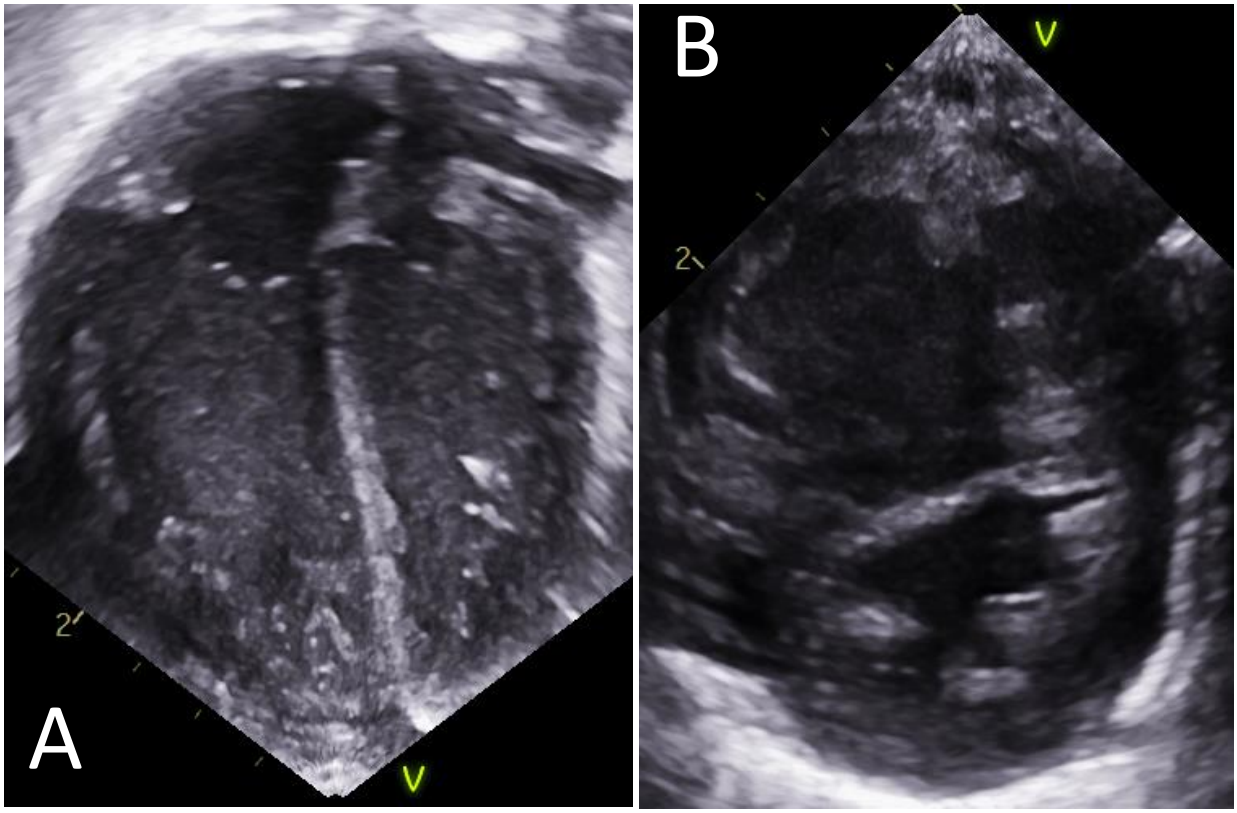
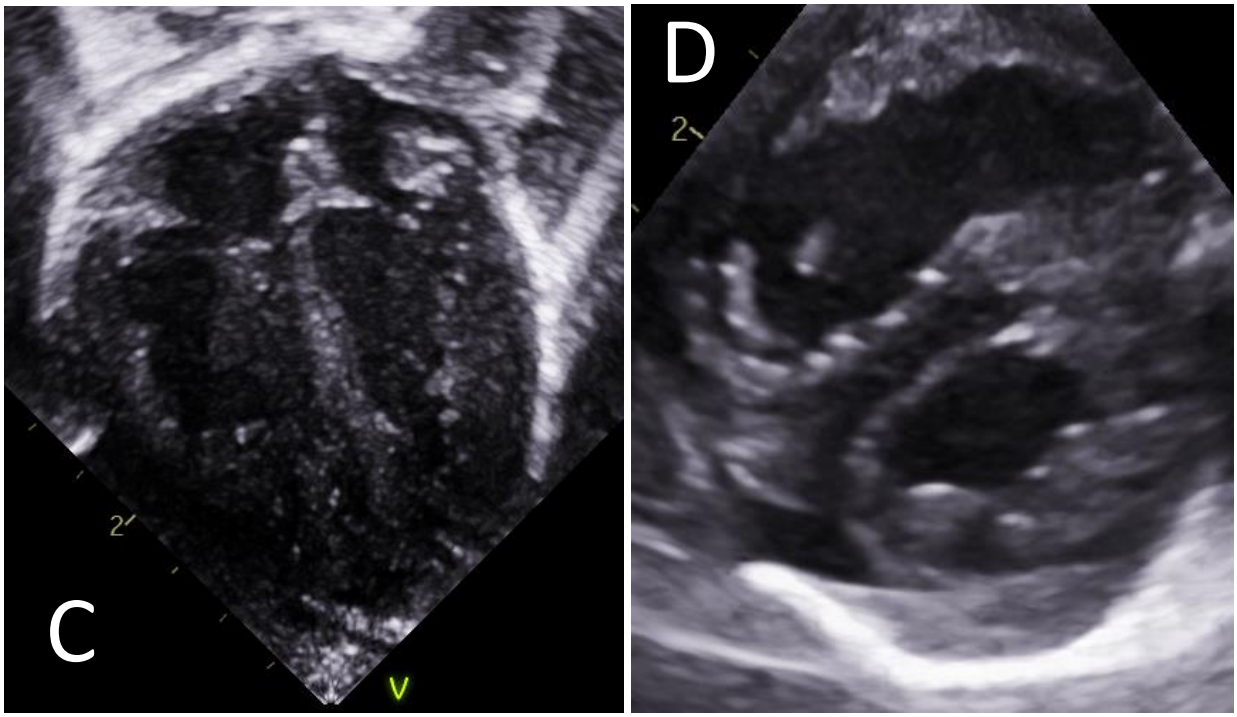
Table 1. Sequential hemodynamic findings on echocardiography

Parameter	DOL 6	DOL 7	DOL 8	DOL 9	DOL 10	DOL 13
LV EDA – 4C (cm^2)	2.29	2.65	2.29	2.14	2.55	3.85
RV EDA – 4C (cm^2)	3.50	3.97	3.92	2.69	2.75	2.97
RV/LV EDA ratio	1.53	1.50	1.71	1.26	1.08	0.77
RVIDd (mm)	17.7	14.4	16.7	9.4	8.8	6.7
Eccentricity index	1.78	2.02	1.77	1.36	1.33	1.33
TAPSE (mm)	5	6.2	7.6	5.3	7.1	10.1
FAC (%)		18	15	25	43	28
Max RVSP* (mmHg)	80	69	73	-	39	35
LVO (ml/min/kg)	101	139	184	148	162	150
RVO (ml/min/kg)	86	210	248	219	269	138
Ductal shunt	Absent	Absent	Minimal, restrictive R-L	Bidirectional	Mostly L-R (75%)	Mostly L-R (75%)
Treatment	At diagnosis	iNO, milrinone	iNO, milrinone, sildenafil (pre-alprostadil)	16 hours after initiation of alprostadil	Alprostadil, sildenafil, MgSO4	Alprostadil, sildenafil

DOL, day of life; LV, left ventricle; EDA – 4C, end diastolic area in apical four chamber view; RV, right ventricle; RVIDd, right ventricle internal dimension in end diastole; TAPSE, Tricuspid Annular Plane Systolic Excursion; FAC, fractional area change; LVO, left ventricular output; RVO, right ventricular output. * Estimated based on a tricuspid regurgitation jet.

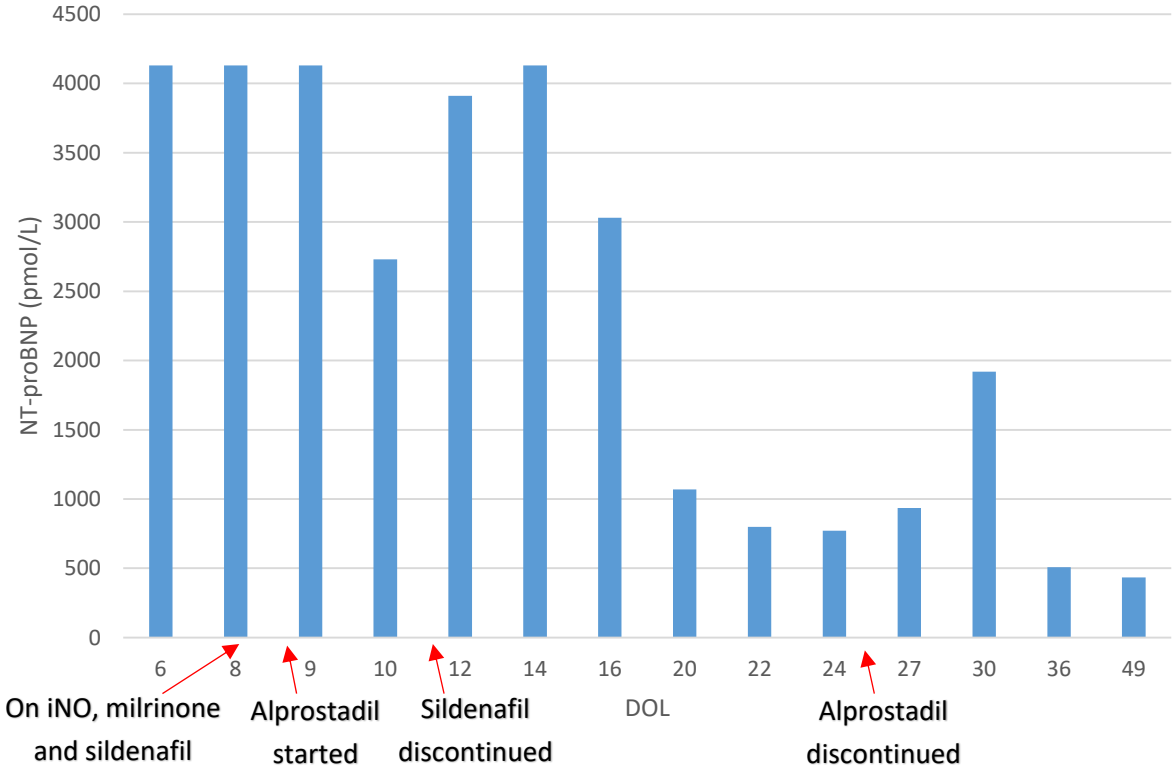
Figure 1. Sequential TNE assessments





A / C– apical four chamber view; B / D - Parasternal short axis view at the level of the papillary muscles. Panels A and B were taken prior to initiation of alprostadil infusion, while the infant was on iNO, milrinone and sildenafil, and demonstrate severe RV dilatation. Panels C and D were captured from a TNE done 16 hours after commencement of alprostadil infusion, and show a major improvement in RV dilatation. Alprostadil infusion was associated with acute reduction in RV dilatation.

Figure 2. Levels of N-terminal pro b-type natriuretic peptide (NT-proBNP) over time



Sequential NT-proBNP levels starting on the day of diagnosis. The data demonstrates a lack of response to multiple pulmonary vasodilators until the introduction of alprostadil. A rebound in pulmonary pressures is also visible once sildenafil was discontinued. DOL, day of life; iNO, inhaled nitric oxide.