NEONATAL HEMODYNAMICS Research Centre

Case Report

Key physiological insight/learning points:

Importance of delineating pulmonary arterial vs pulmonary venous hypertension in the setting of respiratory failure and cardiac dysfunction.

Close attention should be paid to markers of diastolic and systolic function on echo in the transitioning neonate with recommendation for serial evaluation and coordination between neonatal, cardiac, and hemodynamic specialists.

Early cardiogenic support maybe warranted based on hemodynamic markers on echo, despite apparent clinical stability in the transitioning neonate.

A case of neonatal dilated cardiomyopathy and congenital hydrocephalus.

Authors. L Wilson[1], C Bazacliu[2], JL Ruoss[2,3]

Affiliations. Division of Cardiology[1] University of Florida, Gainesville, Fl, USA; Division of Neonatology[2], University of Florida, Gainesville, Fl, USA; Division of Neonatology, Orlando Health Regional Medical Center[3], Orlando, Fl

Background:

We present a case of a late preterm infant with fetal biventricular cardiomegaly, cardiac dysfunction and cranial ventriculomegaly with postnatal biventricular heart failure, respiratory failure, ventricular tachycardia (Vtach), obstructive hydrocephalus, and neonatal seizures.

Neonatal cardiomyopathy has variable fetal and neonatal presentations with morbidity related to the underlying etiology. In a neonate with heart failure, it can be challenging to distinguish whether it is secondary to (1) an extracardiac process - acute pulmonary hypertension (aPH), significant acidosis from sepsis, or high output cardiac failure secondary to an arteriovenous malformation (AVM) or (2) an intrinsic heart disease - myocarditis or cardiomyopathy [1, 2] (table 1). In this case report, we outline the challenging hemodynamic assessment of a neonate with biventricular heart and respiratory failure, expand on the need for serial evaluation, and a multidisciplinary approach to these complex clinical scenarios.

Prenatal and Birth History:

Pregnancy was complicated by fetal cardiomegaly with depressed biventricular function without evidence of hydrops, cranial ventriculomegaly and macrosomia with concern for aqueductal stenosis. Cardiac dysfunction was first noted at 22 weeks gestation without improvement during gestation. Prenatal evaluation including amniocentesis, L1CAM sequencing and deletion/duplication analysis, maternal glucose tolerance test, and TORCH screening were normal. Infant was delivered via c-section at $36^{3/7}$ weeks gestation for preterm labor with abnormal fetal tracing. Delivery was notable for meconium-stained fluid and infant emerged with poor central tone, poor respiratory effort requiring positive pressure ventilation, and ultimate transfer to the neonatal intensive care unit on continuous positive airway pressure (CPAP). APGARs were 7 and 8, at 1 and 5 minutes respectively. Birth weight was 5.53kg (>99th%), head circumference was 47cm (>99th %).

Medical History:

Infant was admitted on CPAP with minimal oxygen requirement. Initial echocardiogram (echo) was notable for elevated right ventricular (RV) pressure by tricuspid valve regurgitation (TR) jet (¾ systolic pressure), low velocity bidirectional patent ductus arteriosus (PDA) shunt, bidirectional shunt across the foramen ovale, right atrium (RA) dilation, RV dilation, RV hypertrophy (RVH), moderate to severe RV dysfunction (TAPSE 0.59cm), left atrial (LA) compression, moderate left ventricular (LV) dilation, moderate left ventricular hypertrophy

(LVH), and severe LV systolic dysfunction (ejection fraction (EF) by Simpsons 33%) with markers of LV diastolic dysfunction (E/A 0.6), and development of mitral valve regurgitation. The clinical presentation of biventricular dilation and dysfunction with elevated pulmonary pressures and in-utero cardiomegaly and dysfunction, raised suspicion of cardiomyopathy as underlying etiology. Despite cardiac dysfunction on admission, the infant was stable with low oxygen requirement on CPAP (fractional inspired oxygen range 35-40% in the first day after birth), no significant metabolic acidosis, appropriate urine output, with initial post-ductal invasive arterial blood pressure of 65/38 (42). The infant was closely monitored with serial echos, arterial blood gas, and lactate. A sepsis evaluation was performed, ampicillin/gentamicin were started and a viral workup for dilated cardiomyopathy was sent (including evaluation for adenovirus, ebstein-barr virus, cytomegalovirus, and SARS-COV2) and were negative. A cranial ultrasound, abdominal ultrasound, and magnetic resonance imaging (MRI) brain were performed to look for an arteriovenous malformation; and were notable for cranial ventriculomegaly. Rapid whole exome sequencing was sent.

In the 24 hours after birth, infant's clinical status deteriorated with increased respiratory distress requiring intubation and surfactant and development of metabolic acidosis with preserved blood pressure. Phenobarbital was started secondary to neonatal seizures confirmed on electroencephalogram and prostaglandin E1 (PGE) was empirically initiated.

Hemodynamic Consultation:

A multidisciplinary bedside approach with neonatology and pediatric cardiology was performed in the setting of acute clinical deterioration and unclear underlying pathology. A limited echo on day 1 revealed qualitative severe RV dysfunction, worsening LV dysfunction (EF 16%), RV pressure remained ¾ systemic based on TR jet, low velocity bidirectional PDA, with stable RV and LV dilation, and no concern for LV outflow tract obstruction. Epinephrine was initiated at 0.05 mcg/kg/min to support cardiac contractility in the setting of metabolic acidosis and declining LV function (EF 33 to 14%). RV dysfunction remained qualitatively unchanged (TAPSE 0.59 cm on the first echo without documentation of a TAPSE or RV fractional area of change on the repeat echo). Hydrocortisone was added for presumed adrenal insufficiency in the setting of multiple anomalies and cardiac dysfunction, cortisol obtained prior to initiation of hydrocortisone was 3.3mcg/dl. Milrinone was not initiated secondary to the blood pressure being at low normal limit and worsening renal function. Infant's respiratory status, blood pressure, perfusion, and metabolic acidosis improved on low dose epinephrine and PGE. Once the blood pressure improved, milrinone was started but was discontinued within 24 hours due to hypotension in the setting of new onset wide complex tachycardia (Vtach).

Over the next 24-48 hours, ongoing improvement was noted in respiratory status, and markers of end-organ perfusion with note of creatinine decreasing from 0.86mg/dl to 0.29 mg/dl and improvement in urine output and metabolic acidosis. PGE was subsequently discontinued. Repeat echo on day 4 noted improvement in RV function and LV function, birdirectional PDA, a previously not visualized perimembranous ventricular septal defect (VSD) was visualized without comment on direction of flow. Diuresis was then initiated for pulmonary vascular congestion noted on chest X-ray, which was thought to be contributed by LV diastolic dysfunction. Unfortunately, due to the challenging windows the echo markers obtained for LV diastolic function (tissue doppler imaging, isovolumic relaxation time) were not able to be obtained.

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Imaging Findings

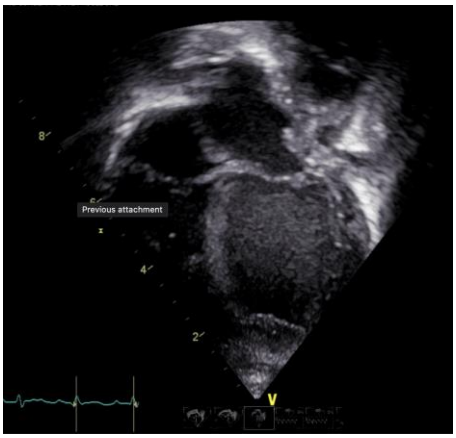

Image 1. Demonstrates dilation of the LV and impaction of the LA on day of birth.

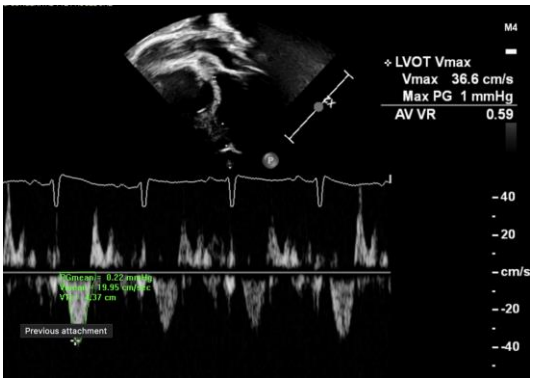

Image 2. Demonstrates low LV output on day of birth

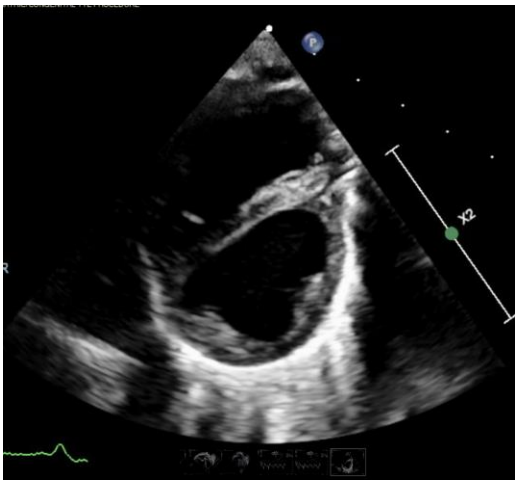

Image 3. Demonstrates dilation of the RV and LV with subjective septal flattening on day 1 after birth.

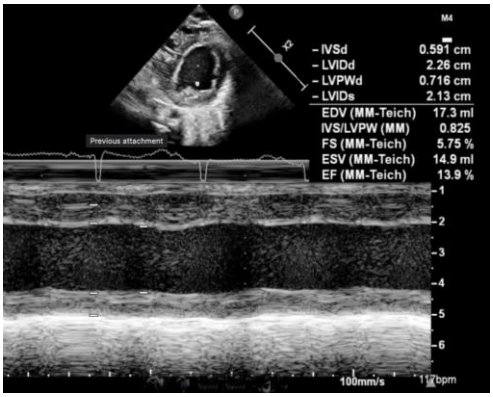

Image 4. Demonstrates severe LV systolic dysfunction on day 1 after birth.

Follow up/ Outcome:

Infant was extubated to CPAP on day 8 and weaned off epinephrine drip on day 10. Ongoing ventricular dysrhythmia necessitated addition of digoxin without further rhythm issues noted. As infant continued to have pulmonary edema and improved but ongoing concern for LV diastolic dysfunction, captopril was added. He underwent a neurosurgical procedure for aquaductal stenosis and gastrostomy tube placement for poor oral intake, tolerating the procedures and general anesthesia well. His echo at time of discharge was notable for normal RV size and systolic function, mild RVH, perimembranous ventricular septal defect (VSD) with small appearing effective orifice and bidirectional flow, mild tricuspid valve regurgitation, mildly dilated LV with mildly decreased LV systolic function, and mild LVH. Whole exome was notable for a pathologic detection of mammalian target of rapamycin (MTOR) gene (c.5930 C>T, p.T1977I), consistent with Smith-Kingsmore syndrome. Infant was discharged home on low flow nasal cannula, digoxin, furosemide, and captopril.

Discussion:

Neonatal cardiomyopathy is a heterogenous disease with a multitude of phenotypes, varying underlying etiologies, and long-term prognosis. Here we present a case of a neonate with dilated cardiomyopathy that was diagnosed early in gestation without progression to hydrops, however with significant deterioration in post-natal life. The whole exome sequence revealed a defect in the MTOR gene consistent with Smith-Kingsmore syndrome, which is associated with epilepsy, macrocephaly, skin pigmentation, developmental delay, and metabolic/nervous system abnormalities [3]. While this syndrome has not previously been associated with cardiac abnormalities, the MTOR gene has a regulatory role in cardiac physiology and development. Several in-vivo studies have demonstrated that MTOR gene deletion is associated with cardiac dilation, cardiac failure, and fetal or early postnatal death [4, 5]. Given that the the whole exome did not report abnormalities in genes typically detected in the cardiomyopathy panel, the likely underlying etiology for cardiomyopathy in this patient is the MTOR gene defect. However, it is important to note that we are limited in our understanding of the genetics of cardiomyopathies. With the testing that is available today, only ~40% of patients with familial dilated cardiomyopathy are detected [2]. While it is possible that the underlying pathology is secondary to prolonged exposure of maternal hyperglycemia (infant of diabetic mother - IDM) this would be an atypical presentation. The typical phenotype for cardiomyopathy in the setting of IDM is hypertrophic not dilated cardiomyopathy and although these infants also improve overtime they are not typically detected as early in gestation.

This case highlights the importance of a hemodynamic approach to infants with cardiogenic and respiratory failure. In this case, neonatologists and pediatric cardiologists worked closely together to re-image and continuously re-evaluate the appropriate management. In assessing infants with aPH and biventricular heart failure, it is important to delineate pulmonary artery HTN from pulmonary venous HTN as management approaches are different. A common cause of neonatal aPH with biventricular dysfunction is due to pulmonary arterial HTN (i.e. meconium aspiration syndrome) in which the RV uncouples from the pulmonary artery through heterotopic adaptation and becomes dilated. The dilated RV can impact the LV by ventriculo-ventricular interactions (LV cavity is decreased, change in LV ellipsoid shape) and ventricular interdependence (RV and LV shared myocardial fibers). In this clinical setting, pulmonary vasodilators can be used to decrease afterload to the RV, improve RV dilation and function, improving LV function. However, using this approach to all newborns with acute respiratory failure and cardiogenic dysfunction could prove deleterious.

In this case, the infant had biventricular ventricular failure, evidence of aPH, with bidirectional PDA shunt, and low oxygen requirements. This infant's clinical phenotype fit more with a dilated cardiomyopathy with biventricular dysfunction and pulmonary venous HTN rather than isolated pulmonary arterial HTN. Inhaled pulmonary vasodilators were discussed as potential treatment secondary to RV dysfunction, RV dilation with impaction of the LA, and close to systemic pulmonary pressures [6]. However, in the setting of stable RV function accompanied by worsening LV dysfunction we raised the concern that the pulmonary HTN could be secondary to pulmonary venous HTN and pulmonary vasodilation could lead to worsening pulmonary edema and further cardiopulmonary compromise [6]. Advanced echo markers including evaluation for LV diastolic dysfunction (tissue doppler imaging, E/A, pulmonary vein A wave, and isovolumic relaxation time), atrial level shunting could be

used to help further delineate pulmonary artery vs pulmonary venous HTN [4]. At 24 hours after birth, the infant's LV function had worsened in comparison to the RV function which further led to concerns for an underlying cardiomyopathy. PGE was empirically added during the acute decompensation, to maintain the PDA and allow the RV to supply part of the systemic blood flow in the setting of presumed severe LV dysfunction. It is important to distinguish pulmonary arterial vs pulmonary venous HTN in case of neonates with hypoxic respiratory failure. In the setting of LV diastolic dysfunction, the myocardial wall tension can be increased to the point that there is elevated ventricular filling pressures which translates into elevated left atrial pressure increasing afterload to the pulmonary venous system resulting in pulmonary venous hypertension. Evaluating the atrial level shunt can be helpful in where a left to right shunt could be indicative of decreased LV compliance in relation to RV compliance. Epinephrine was initiated secondary to its positive inotropy with confirmed severe LV systolic dysfunction and potential systemic vasodilatory effect by action on beta receptors, with caution being used to maintain at low dose in effort to avoid negative side effects. Milrinone was used with caution secondary to ongoing issues with achieving a "normal" diastolic blood pressure, which is needed to achieve appropriate coronary perfusion pressure [4].

This case highlights an atypical presentation of pulmonary HTN, respiratory failure, and cardiac failure associated with obstructive hydrocephalus. We presented a multidisciplinary approach with close serial monitoring and management of a neonate with cardiopulmonary compromise and highlight importance of early genetic evaluation.

Table 1. Neonatal Cardiomyopathy Differential [7, 8]

Phenotype	Potential Etiologies
Dilated cardiomyopathy **LV dysfunction with dilation with pulmonary venous congestion vs biventricular dysfunction with dilation** **Can present with hypoxic respiratory failure, pulmonary venous congestion, and systemic hypotension**	**Genetic:** Inborn Error of metabolism (i.e. neonatal hemochromatosis, mitochondrial oxidative phosphorylation disorders) Myocardial Storage Disorders **Maternal Autoimmune** Neonatal lupus Neonatal thyrotoxicosis **Fetal** Fetal Tachyarrhythmia Severe fetal Anemia **Hypoxic Ischemic** Perinatal asphyxia Anomalous Origin of Left Coronary Artery
Hypertrophic cardiomyopathy **LVH vs LVH/RVH with or without interventricular septum hypertrophy** **Can have hyperdynamic LV and/or LV outflow tract obstruction** **Can present with hypoxic respiratory failure, pulmonary venous congestion, and systemic hypotension.**	**Genetics** As described above **Malformation:** Noonan Syndrome RASopathies Neonatal Overgrowth Syndrome (Bechwith-Weidemann) **Drugs:** Steroids **Maternal Endocrine** Infant of a diabetic **Fetal volume overload** Twin-to-twin
Left ventricular non-compaction cardiomyopathy Trabeculated LV, ventricular dilation, with systolic and diastolic dysfunction	**Genetic**

References:

1. Lee, T.M., et al., *Pediatric Cardiomyopathies.* Circ Res, 2017. **121**(7): p. 855-873.
2. McNally, E.M. and L. Mestroni, *Dilated Cardiomyopathy: Genetic Determinants and Mechanisms.* Circ Res, 2017. **121**(7): p. 731-748.
3. Besterman, A.D., et al., *Functional and structural analyses of novel Smith-Kingsmore Syndrome-Associated MTOR variants reveal potential new mechanisms and predictors of pathogenicity.* PLoS Genet, 2021. **17**(7): p. e1009651.
4. Jain, A., et al., *Care of the critically ill neonate with hypoxemic respiratory failure and acute pulmonary hypertension: framework for practice based on consensus opinion of neonatal hemodynamics working group.* J Perinatol, 2022. **42**(1): p. 3-13.
5. Sciarretta, S., M. Volpe, and J. Sadoshima, *Mammalian target of rapamycin signaling in cardiac physiology and disease.* Circ Res, 2014. **114**(3): p. 549-64.
6. Ruoss, J.L., et al., *Management of cardiac dysfunction in neonates with pulmonary hypertension and the role of the ductus arteriosus.* Semin Fetal Neonatal Med, 2022: p. 101368.
7. Jayaprasad, N., *Heart Failure in Children.* Heart Views, 2016. **17**(3): p. 92-99.
8. Moulik, M., *Neonatal Cardiomopathies.* 2016.