

# Subclinical Left Ventricular Systolic Dysfunction due to Coronary Arterial Thrombosis in a Neonate with Hypoxic Ischemic Encephalopathy Undergoing Therapeutic Hypothermia



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## INTRODUCTION

The use of targeted neonatal echocardiography (TnECHO) performed by neonatologists as part of hemodynamics consultation is becoming increasingly more common in neonatal intensive care units around the world. These assessments offer physiological insights to help enhance diagnostic precision, guide the selection of therapies, and monitor treatment response in the care of critically ill newborns.<sup>1</sup> In many instances in neonatology, TnECHO is also used as a screening tool to detect physiological disturbances that may be subclinical yet negatively impact vulnerable organ performance. In particular, routine screening assessment for patent ductus arteriosus and chronic pulmonary hypertension in preterm infants is the standard of care in many neonatal intensive care units.<sup>2</sup> Recent observational evidence highlights the association of hypoxic ischemic encephalopathy (HIE), despite initiation of therapeutic hypothermia (TH), with a higher incidence of hemodynamic derangements including pulmonary hypertension and right ventricular (RV) systolic dysfunction. More importantly, the presence and severity of right heart failure in particular has been associated with increased risk of death, abnormal magnetic resonance imaging, and adverse neurodevelopmental outcome.<sup>3,4</sup> This finding is independent of illness severity or magnitude of primary hypoxic-ischemic insult. Earlier identification, monitoring, and optimization of RV systolic dysfunction may positively impact neonatal outcomes. In our institution, screening TnECHO is performed on all infants with moderate to severe HIE who are undergoing TH on the first postnatal day regardless of the clinical cardiorespiratory state.

## CASE PRESENTATION

The index case was a term neonate born by emergent cesarean section at a community hospital who required extensive resuscitation af-

ter birth; specifically, positive pressure ventilation, intubation, chest compressions for 8 minutes, and 2 doses of epinephrine (1 endotracheally and 1 intravenous) were required. Apgar scores were 1, 3, 2, 1, 1, and 5 at 1, 5, 10, 15, 20, and 25 minutes, respectively (normal Apgar  $\geq 7$ ). Cord blood gas testing revealed an arterial pH of 7.07 and a base deficit of 11 (normal base deficit  $\geq -3$ ). The 1-hour postnatal arterial lactic acid level was 16.6 mEq/L. The initial neurologic examination was consistent with a diagnosis of moderate HIE; therefore, he was transferred to a quaternary neonatal intensive care unit for initiation of TH. Upon arrival he was placed on synchronized intermittent mandatory ventilation (peak inspiratory pressure, 10; positive end-expiratory pressure, 5; respiratory rate, 15; fraction of inspired oxygen, 0.21). An arterial blood gas showed compensated metabolic acidosis (pH, 7.37; pCO<sub>2</sub>, 18 mm Hg; PaO<sub>2</sub>, 57 mm Hg; base deficit, 15) with an elevated plasma lactic acid of 8.2 mEq/L. Right arm arterial pressure (63/43 [49] mm Hg) and heart rate (115 bpm) were both within a normal range ( $\geq 55/30$  mm Hg, 100-160 bpm). Whole-body TH, using the Criticool thermal regulating system (Belmont Medicals Technologies, Billerica, MA), was initiated (target core temperature 33.5 °C) after 4 postnatal hours. Indices of cardiorespiratory instability including arterial pressure, heart rate, and the efficacy of oxygenation remained stable, and he received no cardiovascular support. As per the unit's protocol, the infant underwent routine comprehensive TnECHO at 14 hours to assess heart function and pulmonary hemodynamics in the setting of moderate HIE. Comprehensive echocardiography evaluation of heart function, pulmonary and systemic hemodynamics, and shunt flow patterns, as well as anatomic surveillance, were performed according to a standardized protocol (Table 1).

On echocardiography assessment, an echogenic focus was seen in the aortic root, which was suspicious for a thrombus in the ostium of the left coronary artery (Figure 1, Videos 1-3). There was evidence of severe left ventricular (LV) systolic dysfunction; specifically, LV ejection fraction (Simpson's biplane method) of 28% and peak longitudinal strain of -3.6% on the apical 4-chamber view (Figure 2, Videos 4 and 5) were noted. Left ventricular output was estimated to be 57 mL/min/kg, and the patent ductus arteriosus measured 4.6 mm with bidirectional shunt. He was treated with intravenous epinephrine (maximum dose, 0.08  $\mu$ g/kg/min), dobutamine (maximum dose, 5  $\mu$ g/kg/min), and milrinone (maximum dose, 0.75  $\mu$ g/kg/min) infusions. Opening troponin T was 12.02 ng/mL (normal, 0.01-0.062 ng/mL), and an electrocardiogram showed prominent Q wave in I and augmented vector left with ST elevations in lateral precordial leads concerning for left coronary ischemia. The infant underwent coronary angiography that confirmed thrombus in the proximal left anterior descending and circumflex coronaries and received intracoronary alteplase. Therapeutic hypothermia was maintained for a total of

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## VIDEO HIGHLIGHTS

**Video 1:** Suprasternal notch short-axis transthoracic echocardiography view (crab view) showing extensive thrombus in the emergence of the left coronary artery.

**Video 2:** Parasternal long axis with echogenic focus at the level of the aortic root.

**Video 3:** Parasternal short axis with echogenic focus in the ostium of the left coronary artery and bicuspid aortic valve.

**Video 4:** Apical 4-chamber view showing significantly reduced LV systolic function with an estimated ejection fraction of 28% by Simpson's biplane.

**Video 5:** Two-dimensional speckle-tracking imaging of the apical 4-chamber view with longitudinal strain analysis showing significantly reduced LV systolic function (single plane longitudinal strain, -3.6%).

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72 hours, which was followed by graduated rewarming, according to a standardized protocol, both occurring without any significant clinical decompensation. Indices of LV systolic function recovered slowly (LV ejection fraction of 37% on discharge), and he was discharged home on carvedilol and enalapril. His neurologic exam upon discharge was within normal limits, and brain magnetic resonance imaging after rewarming showed no findings suggestive of hypoxic-ischemic insult. At 6 months, his LV ejection fraction was 45% and he remained clinically stable.

## DISCUSSION

Heart dysfunction is a clinically important consequence of HIE that impacts the likelihood of brain injury but may be clinically silent. Early identification of subclinical LV dysfunction and timely implementation of physiologically targeted cardiovascular agents, with predominant inotropic and vasodilator properties, led to LV recovery and avoidance of profound clinical deterioration. Most importantly, there was no evidence of hypoxic-ischemic brain injury on magnetic resonance imaging evaluation. There are 3 important considerations in this case that are relevant for clinicians involved in the cardiovascular care of neonates with a diagnosis of HIE who are receiving TH. The first is the merits of screening echocardiography in this high-risk population even in the absence of significant clinical concerns. Prior studies have highlighted the relationship of RV dysfunction as an independent predictor of brain injury, despite TH.<sup>4</sup> At the time of screening TnECHO, there was no evidence of hypotension, tachycardia, features of low cardiac output state, or myocardial dysfunction. Although the initial lactate was elevated, this is an expected finding in the setting of HIE due to primary energy failure and anaerobic metabolism.<sup>5</sup> In addition, urinary output is a poor marker of low cardiac output state in the setting of HIE due to direct renal injury.<sup>6</sup> The index

case presented with an atypical finding of predominant LV dysfunction, which was not clinically apparent at the time of echocardiographic assessment. It is highly likely that a delay in diagnosis could have resulted in worse clinical trajectory and outcome.

Second, it is possible that TH may have modulated myocardial oxygen consumption in the setting of significant myocardial ischemia and minimized the impact on the clinical presentation. Therapeutic hypothermia has cardioprotective effects in both human and animal models, with reduction of troponin I levels and improvement in ischemic heart lesions.<sup>7</sup> The secondary reduction in heart rate may also result in decreased myocardial substrate requirement and LV output, minimizing further ischemic injury. Importantly, although cardiac output is lower, this is usually well tolerated and meets the metabolic demands of the asphyxiated newborn in the context of TH.<sup>3</sup> Finally, most neonates undergoing TH have normal or slightly increased blood pressure due to hypothermia-induced vasoconstriction.<sup>8</sup>

Third, rigorous training for neonatologists performing echocardiograms and close collaboration with pediatric cardiology is imperative to provide high-quality care to vulnerable neonates. We have previously shown that first echocardiograms performed by subspecialty neonatologists provide imaging of sufficient quality to evaluate critically unwell neonates with low suspicion for critical congenital heart disease.<sup>1</sup> While the primary aim of the TnECHO assessment is to obtain physiologic information related to heart function, shunts, and systemic and pulmonary hemodynamics, comprehensive anatomical surveillance is performed in parallel. All members of the neonatal team who acquire echocardiography information have completed at least basic TnECHO training. Although detailed coronary imaging is not necessarily mandated in the first assessment, these images are obtained in cases of significant left heart dysfunction as part of the differential diagnosis. Imaging necessary for strain is obtained as part of the TnECHO assessment but not routinely analyzed (Table 1); it is, however, an adjunct measurement for longitudinal assessment of LV systolic dysfunction. In addition, any patient assessed by the neonatal hemodynamics team must have a full anatomical scan performed by the cardiology team prior to discharge from the neonatal intensive care unit. If any structural defects are suspected, as occurred in this case, the neonatal hemodynamics team immediately informs the attending neonatologist and organizes imaging review and consultation with pediatric cardiology.

## CONCLUSION

This case highlights the merits of echocardiography screening in neonates at high risk for myocardial dysfunction, even in the absence of clinical instability. It also highlights the importance of rigorous training for neonatologists performing echocardiograms and close collaboration with pediatric cardiology.

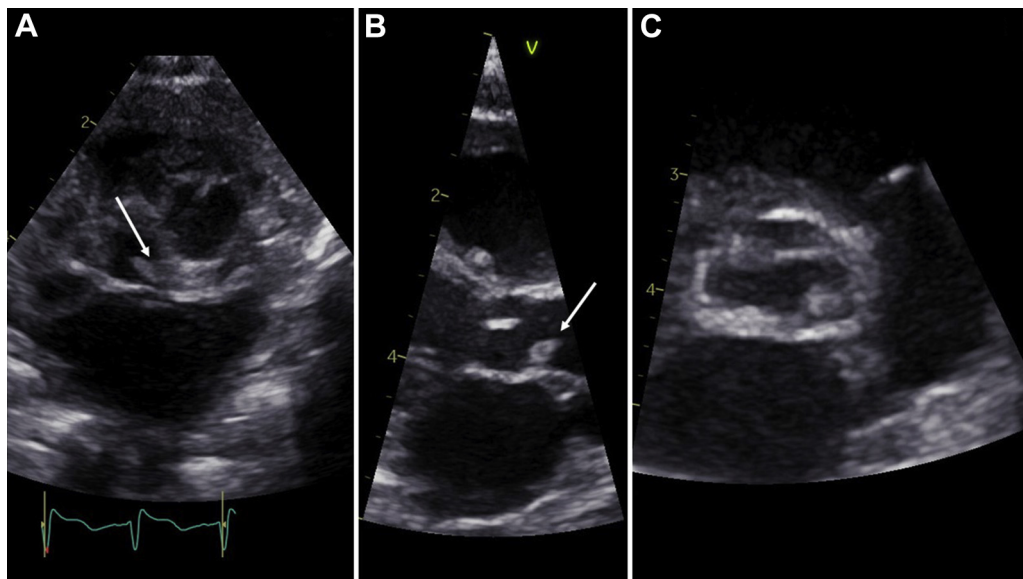
## SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.case.2022.04.008>.

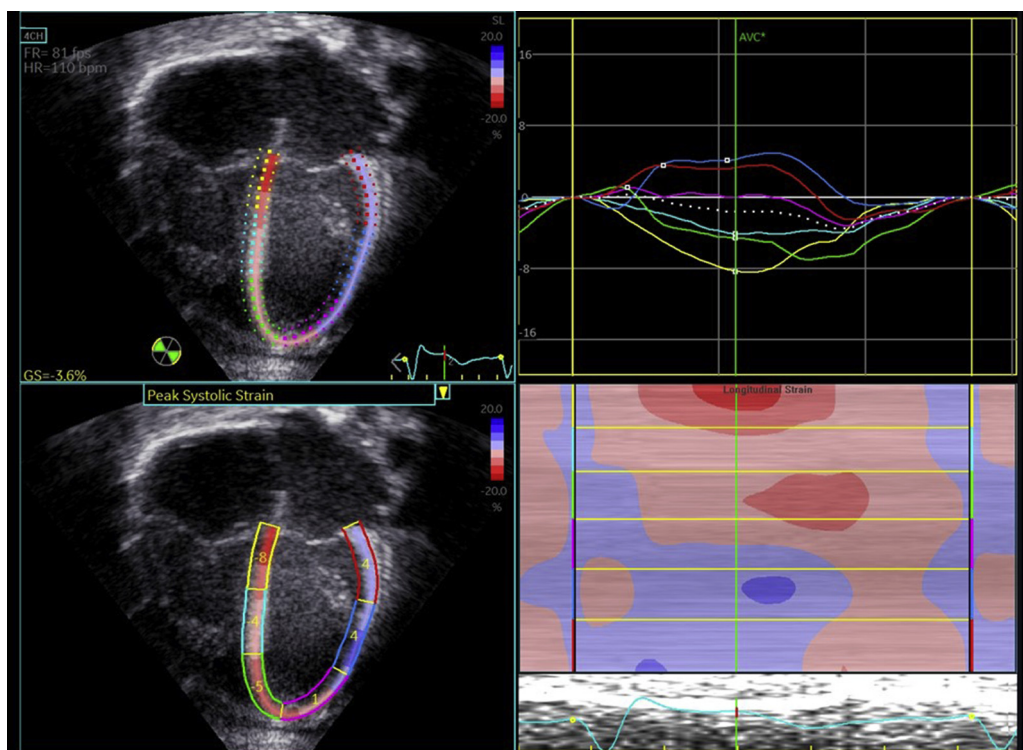
**Table 1** TnECHO first echocardiogram protocol<sup>1</sup>

View	Structure	Function
Apical 4-, 2- and 3- chamber	Both ventricles reaching the apex. Opening mitral and tricuspid valves. Establish atrioventricular concordance. Assessment of IVS. Rotate to 5-chamber view to identify normal aortic valve from the left ventricle. Demonstrate pulmonary artery from the right ventricle crossing over, excluding transposition. Pulmonary veins draining into left atrium.	Ejection fraction using Simpson's biplane method. Mitral and tricuspid inflow patterns. TR jet. Pulmonary vein inflow. LV outflow tract VTI. May be used for tissue Doppler imaging and strain imaging. Tricuspid annular plane systolic excursion.
Apical right ventricle 3-chamber view	Right ventricle inflow and outflow.	RV fractional area change
Parasternal long axis	Normal motion of aortic and mitral valves. Assessment of IVS. Identify normal tricuspid and pulmonary valves.	Aortic and pulmonary valve annulus. RV outflow tract VTI. M mode for fractional shortening. M mode for left atrium:aorta ratio. TR jet.
Parasternal short axis	Identify normal tricuspid, aortic, and pulmonary valves. Assessment of IVS. Identify bifurcation of pulmonary artery into confluent left and right branches. Check ductal patency and direction of flow.	Septum morphology. TR jet. M mode for fractional shortening. RV outflow tract VTI. PDA diameter, flow direction, and velocity.
Arch/ suprasternal notch view	Normal arch. Exclude interrupted aortic arch and coarctation, including Doppler flow profile. Verify aortic sidedness. Confirm drainage of pulmonary veins into the left atrium ("crab" view).	Descending aortic diastolic flow.
Ductal	Check ductal patency and direction of flow.	PDA diameter, flow direction, and velocity.
Subcostal	Inferior vena cava and SVC drainage into the right atrium. Pulsatile descending aorta. Assessment of interatrial septum.	Direction of patent foramen ovale/atrial septal defect shunt. Descending aortic diastolic flow. SVC flow.

IVS, Interventricular septum; PDA, patent ductus arteriosus; SVC, superior vena cava; TR, tricuspid regurgitation; VTI, velocity-time integral.



**Figure 1** (A) Suprasternal notch short-axis transthoracic echocardiography view (crab view) showing extensive clot (*arrow*) in the emergence of the left coronary artery. (B) Echogenic focus (*arrow*) seen on parasternal long axis at the level of the aortic root. (C) Echogenic focus on parasternal short axis at the ostium of the left coronary artery.



**Figure 2** Single-plane longitudinal strain analysis from the apical 4-chamber view showing significantly decreased LV systolic function in all the segments with a peak longitudinal strain of  $-3.6\%$ .

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