Lethal Myocardial Infarction in a Neonate During Extracorporeal Membrane Oxygenation

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a lifesaving intervention for neonates born with congenital diaphragmatic hernia (CDH), which is the most common neonatal indication for its use.[1] It is, however, a high-risk treatment modality that is frequently complicated by the need to carefully manage the coagulation balance, between the risk of bleeding and clotting, in neonates due to multiple factors such as developmental hemostasis, differences in primary hemostasis, heparin resistance, and inflammation.[2] Although guidelines have been published to guide anticoagulation management in neonates, there is significant variation in practice.[3]

In neonatal cardiac ECMO, thrombotic events are frequently reported (29%).[4] Data regarding patient-related thromboembolic events and specifically intracardiac thrombosis (ICT) in neonatal venoarterial (VA) ECMO are limited. Of note, ICT with VA-ECMO has been reported in pediatric and adult patients and is associated with severe cardiac dysfunction with subsequent myocardial infarction (MI) and high mortality; however, neonatal data are limited.[5] We present a case of severe left ventricular (LV) dysfunction due to complete occlusion of the left main coronary artery (LMCA) secondary to a large clot extending from the arterial cannula.

CASE PRESENTATION

A term baby was born at a gestational age of 39 5/7 weeks with known fetal CDH via spontaneous vaginal delivery. Prenatal ultrasound showed a moderate-risk left-sided CDH with bowel, stomach, and left lobe of the liver within the chest (lung area to head circumference ratio 1.38 with observed to expected ratio of 43%). Prenatal genetic testing via amniocentesis showed a normal female on karyotype and chromosome microarray and negative aneuploidy on FISH. A fetal echocardiogram was performed, which noted a structurally normal fetal heart with dextroposition, normal ductal arch, and inadequate visualization of the ascending aorta. Maternal history was otherwise noncontributory. The delivery was complicated by the presence of a nuchal cord. The patient was intubated at birth due to the known prenatal diagnosis and had Apgar scores of 7 and 8 at 1 and 5 minutes, respectively. As per the unit's protocol, high-frequency oscillator ventilator was initiated immediately after birth. The patient underwent a comprehensive targeted neonatal echocardiogram (TNE) assessment within the first 2 hours after birth that showed severe pulmonary hypertension and biventricular dysfunction in the presence of a patent ductus arteriosus with right-to-left shunt and patent foramen ovale with bidirectional shunt (Video 1). The patient was treated with inhaled nitric oxide, intravenous milrinone, and intravenous epinephrine. The aortic arch initially measured small, with the aortic isthmus measuring 2.5 mm (Z score = −3.98, normal = 3.36-5.95); however, over the course of the first week, once the patient was hemodynamically more stable, the measurements were noted to be within normal limits. Echocardiogram prior to the CDH repair showed systemic level pulmonary hypertension in the presence of a large bidirectional transductal shunt (predominant left-to-right flow (59% by velocity-time integral, 72% by time) and normal biventricular systolic function.

The patient underwent surgical repair of the CDH on the sixth postnatal day. The immediate postsurgical course was uneventful; however, the patient developed progressive oxygenation and ventilation failure, which was exacerbated by multiple pneumothoraces that required chest tube placements. Despite the addition of multiple pulmonary vasodilators (intravenous alprostadil and sildenafil), diuresis (intravenous furosemide infusion), and anti-inflammatory medications (intravenous aminophylline and methylprednisolone), the patient developed refractory hypoxemic respiratory failure and worsening of the pulmonary hypertension for which VA-ECMO was initiated on postnatal day 25. Continuous veno-venous hemodialysis was introduced to the circuit on the ECMO day 6 to optimize fluid balance. The clot burden steadily increased in the circuit despite adjustments to the anticoagulation therapy per the unit's protocol and led to a circuit change on ECMO day 8. The patient, however, remained coagulopathic with signs of platelet consumption (platelets 19k-79k/mm^3, partial thromboplastin time 45 to 73 seconds, unfractionated heparin anti-Xa 0.15-0.16 U/mL). A head and renal ultrasound on ECMO day 9, obtained to evaluate for clots, was reported as negative.

The patient developed an acute episode of severe systolic and diastolic hypotension later on ECMO day 9 that was unresponsive to fluid boluses and high doses of inotropic (intravenous epinephrine) and vasopressor (intravenous norepinephrine and vasopressin) support. The arterial cannula terminated at T6 (it was at T5 on initial placement) on chest radiograph (Figure 1) and was therefore adjusted, but without impact. The circuit was reported to be intact, and flow was increased from a baseline

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VIDEO HIGHLIGHTS

Video 1: Two-dimensional TNE, apical 4-chamber view, demonstrates severe biventricular systolic dysfunction.
Video 2: Two-dimensional transthoracic echocardiography, parasternal short-axis sweep view to a parasternal long-axis view, demonstrates a clot extending from the ascending aorta into the LV cavity.
Video 3: Two-dimensional transthoracic echocardiography, parasternal long-axis view, demonstrates the arterial cannula extending deep into the proximal ascending aorta.
Video 4: Two-dimensional transthoracic echocardiography with color-flow Doppler (reduced Nyquist limit), parasternal short-axis view, demonstrates no evidence of flow in the LMCA.
Video 5: Two-dimensional transthoracic echocardiography, apical 5-chamber view, demonstrates that the aortic valve was not opening at any point during the cardiac cycle.

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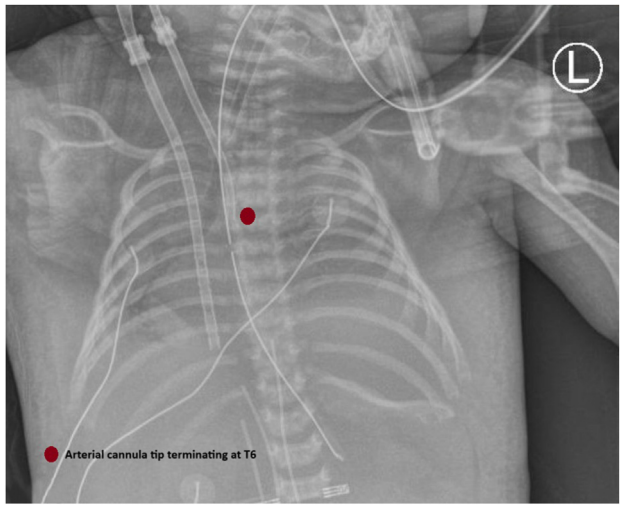

Figure 1 Chest radiograph, anterior-posterior projection, demonstrates the VA-ECMO cannula positions *(red circles)* with the arterial cannula tip terminated at T6, which was deeper than its location at insertion.

of 100 mL/kg/day to 130 mL/kg/day. A limited TNE was emergently performed to evaluate cannula position and heart function and revealed severely reduced LV ejection fraction (<10%; biplane Simpson), no detectable forward flow, and a large thrombus in the proximal aorta. The thrombus was noted to be near the arterial cannula, extended to the aortic cusps, and was adjacent to the origin of the LMCA (Figure 2, Video 2). Of note, the arterial cannula was noted to be deep and extended into the proximal aorta (Figure 3, Video 3). The images were reviewed, and the findings confirmed by the on-call cardiologist. A pediatric cardiology echocardiogram further demonstrated that the aortic valve was not opening in systole, with blood flow visualization in the proximal right coronary artery but not in the LMCA (Figures 4 and 5, Videos 4 and 5). The patient's electrocardiogram rhythm strip showed evidence of ST-segment elevation and intermittent ectopic beats (Figure 6). Troponin T obtained at that time was 220 ng/L (normal reference range, ≤93 ng/L). An urgent multidisciplinary discussion, which included the neonatologist, neonatal hemodynamics specialist, pediatric cardiologist, and pediatric cardiac surgeon, was held, and further interventions were deemed to be futile due to the poor prognosis. Findings were discussed with the family, who opted for compassionate withdrawal of care.

DISCUSSION

Neonatal patient-related cardiac thromboembolic events on VA-ECMO are not well described in the literature. The Extracorporeal Life Support Organization database reports thrombosis as a complication largely as a circuit-related event and focuses on only 2 patient-related thrombotic complications: intracranial and limb ischemia, both with reported incidence of <2%.[6] The BATE study provides some details regarding neonatal thrombotic complications, with an incidence of 13% (most commonly intracranial [4.5%] and limb [3.4%] ischemia).[4] There were no cases of neonatal ICT at these 8 sites in comparison with the pediatric population, in which 9 cases were reported. Of the 23 circuit-related thrombotic events in neonatal cardiac ECMO, 1 patient had a clot seen at the arterial cannula similar to the index case. The morbidity and mortality in the aforementioned neonatal cases has not been described; however, literature from the adult population suggests ICT on VA-ECMO is a very high-risk complication. A case series demonstrated that the clot formation was typically left sided, with severely depressed LV function.[5] Of the 12 cases, 10 patients died due to neurological injury or severe multiorgan failure resulting in withdrawal of care.

The development of VA-ECMO-associated ICT could be multifactorial such as an imbalance between endogenous procoagulant and anticoagulant factors, insufficient systemic anticoagulation, and significant intracardiac and intra-aortic blood stasis, all contributing to a prothrombotic state. While some of these challenges are intrinsic to neonatal anticoagulation therapy, the case described herein possibly had additional risk factors. Isolated aortic arch anomalies are present in 7% of CDH patients and are associated with higher mortality.[7] A case of left-sided CDH who developed LV dysfunction and MI has been described before in which the autopsy demonstrated a small aortic valve and ascending aorta and hypoplasia of the distal aortic arch and isthmus.[8] This patient's aortic arch initially measured on the smaller side and could have contributed to the blood flow stasis and a resultant arterial cannula clot. The deep position of the arterial cannula in a patient with arch hypoplasia may also be a predisposing factor to the clot formation. Echocardiography has been described as a better imaging modality in identifying correct positioning of the cannulas in neonatal ECMO.[9] At our center, ECMO patients undergo TNE assessments daily for the first 5 to 7 days and thereafter based on clinical status.

Neonatal MI is a rare, life-threatening condition with a high mortality rate reported in cases secondary to a coronary thrombus (90%).[10] The ability to determine coronary flow is crucial and can be challenging due to the acute clinical deterioration, as was seen in this case. The Nyquist limit can be crudely altered by decreasing the color scale to better visualize the low velocities associated with coronary flow. Apart from the initial management for hemodynamic instability, which is focused on inotropic support and afterload reduction, various definitive treatments have been described in the

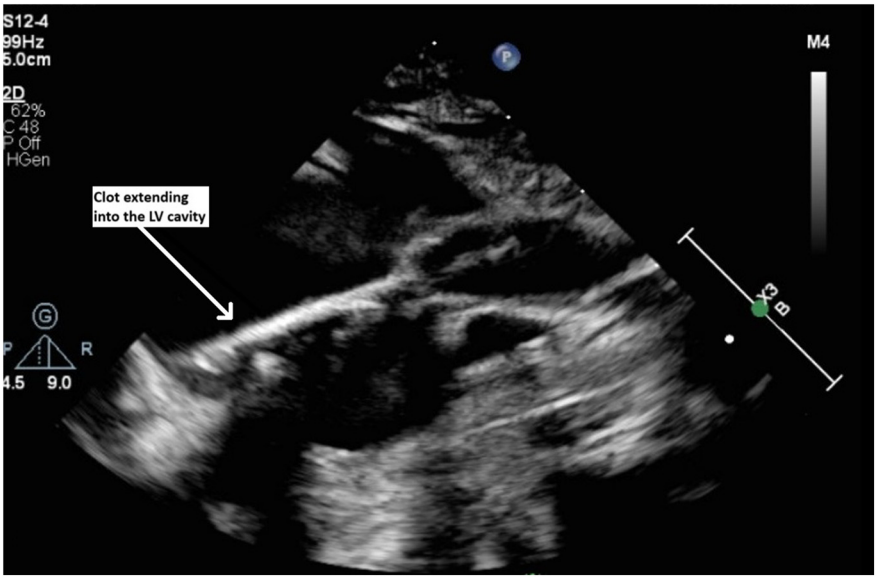

Figure 2 Two-dimensional transthoracic echocardiography, parasternal long-axis view, demonstrates a clot extending from the proximal ascending aorta into the LV cavity.

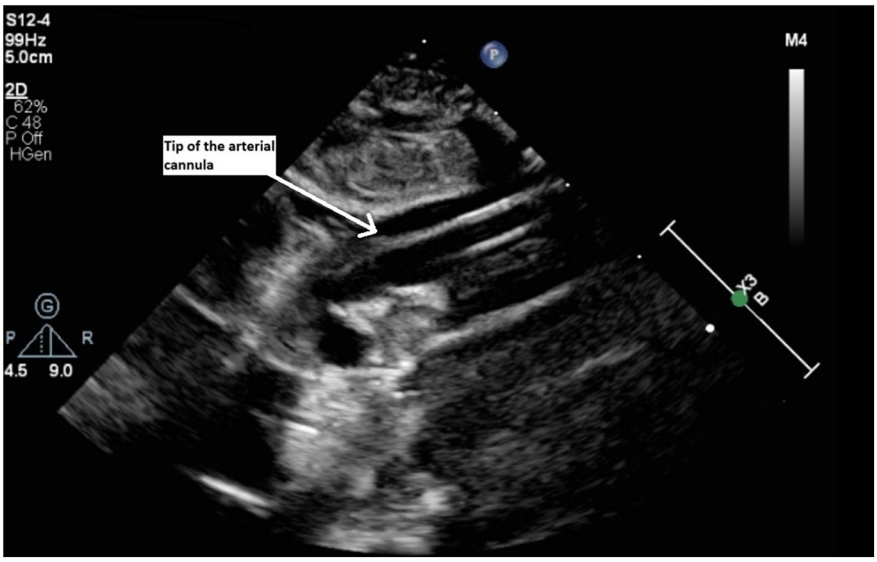

Figure 3 Two-dimensional transthoracic echocardiography, parasternal long-axis view, demonstrates the arterial cannula extending deep into the proximal ascending aorta.

literature. These include surgical thrombectomy, interventional catheterization, and administration of thrombolytic therapies followed by systemic anticoagulation.[11,12] Extracorporeal membrane oxygenation and LV assist devices have also been utilized as additional support for stabilization. Recent literature supports the use of intracoronary recombined tissue plasminogen activator followed by intravenous heparin administration.[13] Ultrasound-enhancing agents can aid in highlighting obstructed coronary flow and may improve microvascular flow with ultrasound impulses.[14] The 2018 American Society of Echocardiography guidelines supported the use of these agents in pediatric patients. There are currently no data available regarding their routine clinical use in neonates.[15] Furthermore, the effectiveness of these therapies is hard to determine in neonates who remain hemodynamically unstable while on maximal medical support such as the neonate in this case, who was already on VA-ECMO and systemic anticoagulation.

CONCLUSION

Anticoagulation therapy in neonatal VA-ECMO can be challenging. In particular, CDH patients with LV outflow tract obstruction may be at higher risk for developing intracardiac thrombotic events, which are

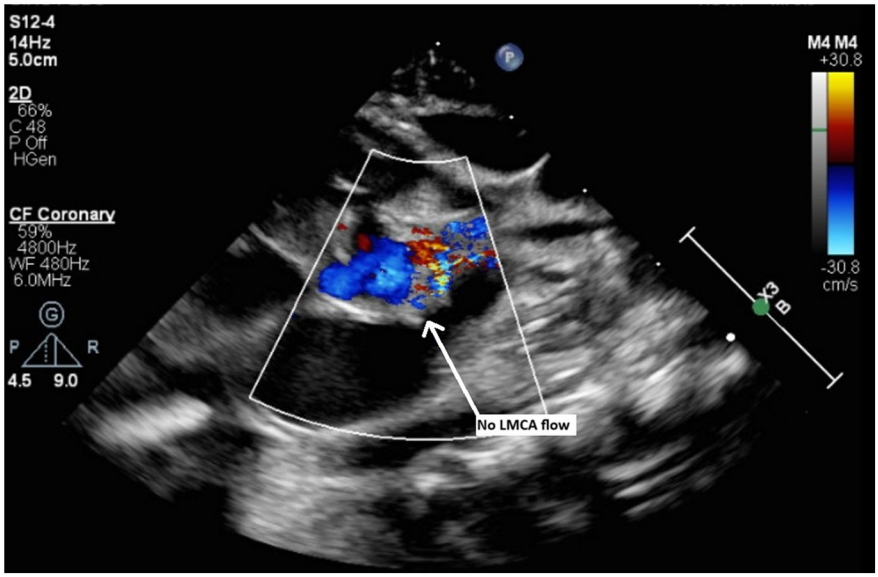

Figure 4 Two-dimensional transthoracic echocardiography with color-flow Doppler (reduced Nyquist limit), parasternal short-axis view, demonstrates no evidence of flow in the LMCA.

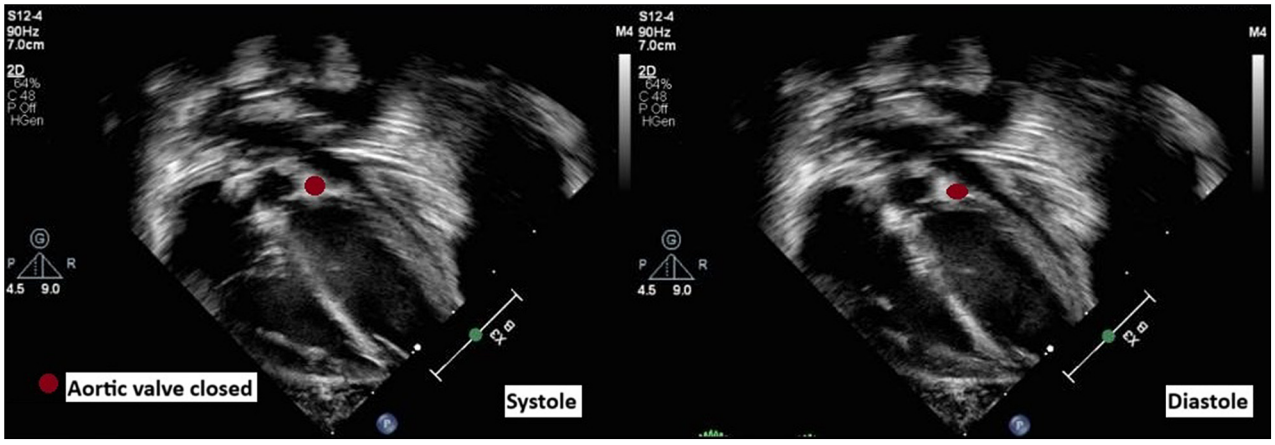

Figure 5 Two-dimensional transthoracic echocardiography, apical 5-chamber view in systole *(left)* and diastole *(right)*, demonstrates that the aortic valve *(red circle)* was not opening at any point during the cardiac cycle.

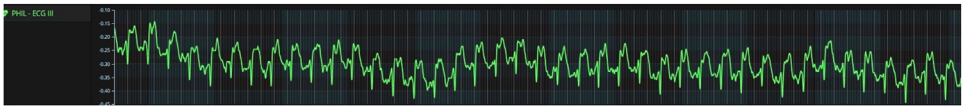

Figure 6 Electrocardiographic rhythm strip recording (precordial lead V2) during clinical deterioration demonstrates marked ST-segment elevation.

associated with high mortality. Of note, TNE can be an effective tool, not only as a way of determining cardiac function in ECMO patients but also for serial monitoring of cannula position and facilitating earlier detection of clot formation as a means to mitigate the risk of major clot propagation.

ETHICS STATEMENT

The authors declare that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

CONSENT STATEMENT

The authors declare that since this was a non-interventional, retrospective, observational study utilizing de-identified data, informed consent was not required from the patient under an IRB exemption status.

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DISCLOSURE STATEMENT

The authors report no conflict of interest.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2024.10.003.

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