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Case report

# Hemodynamics guided care during extracorporeal membrane oxygenation (ECMO): a case report

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## Abstract

Congenital diaphragmatic hernia (CDH) represents a population of high risk of major cardiopulmonary decompensation. Maintenance of patency of the patent ductus arteriosus (PDA), using intravenous prostaglandin, is a strategy used by some clinicians to decrease the risk of right ventricular dysfunction. A term infant with CDH presented with pulmonary hypertension unresponsive to aggressive hemodynamic support. Within 12 hours of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) initiation, circuit chugging occurred that was refractory to multiple volume boluses. Targeted neonatal echocardiography (TnECHO) revealed a high-volume left-to-right shunt across the PDA, resulting in decreased blood return to the right atrium. Interventions aimed at reducing the left-to-right PDA shunt led to the resolution of circuit chugging. This report highlights the unique challenge of VA-ECMO flow in the setting of a large PDA and the consequences of interventions, increasing PDA diameter or lowering pulmonary vascular resistance, on the magnitude of systemic-pulmonary shunting and systemic blood flow. TnECHO played a vital role in monitoring hemodynamics and guiding ECMO adjustments.

## Keywords

Congenital diaphragmatic hernia (CDH), extracorporeal membrane oxygenation (ECMO), patent ductus arteriosus (PDA), targeted neonatal echocardiography (TnECHO).

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## Introduction

Congenital diaphragmatic hernia (CDH) is the most common non-cardiac indication for neonatal extracorporeal membrane oxygenation (ECMO) [1]. The pathophysiology of CDH includes both lung hypoplasia and pulmonary vascular remodeling leading to refractory pulmonary hypertension (PH) [2]. In addition, patients with CDH are at increased risk of heart dysfunction and aortic arch hypoplasia, which can further complicate the clinical course [3-4].

Severe PH is a life-threatening physiologic state in CDH infants, leading to right ventricle failure, particularly when the patent ductus arteriosus (PDA) becomes restrictive [5]. *In utero*, the PDA connects the pulmonary artery to the aorta and plays a vital role in fetal circulation. After birth, the ductus arteriosus (DA) will close during a normal postnatal transition; however, in the setting of severe PH and elevated right ventricular afterload, it may lead to right ventricular dysfunction, which further compromises pulmonary blood flow. The use of intravenous prostaglandin E1 (PGE1) in CDH infants has been shown to improve the efficacy of oxygenation and the adequacy of both pulmonary and systemic blood flow in neonates with refractory PH [6]. Physiologically, this may relate to the pulmonary vasodilator properties of PGE1 or its effects on reopening the DA, which will offload a pressure/volume-loaded right ventricle. Thus, unlike pediatric or adult patients, many neonates will have a wide-open PDA during the ECMO run; therefore, variance in flow patterns across the DA, according to ambient physiologic conditions, may complicate the hemodynamics of neonates on ECMO by altering cardiac loading conditions. Animal experimental studies have highlighted that a large left-to-right shunt may be a cause of critical deterioration on ECMO [7]. In humans, prolonged exposure to a left-to-right PDA shunt is associated with pulmonary edema and longer ECMO duration [8, 9]. These studies have not investigated the relationship of magnitude of left-to-right shunt across the PDA on the adequacy of systemic blood flow and the efficiency of ECMO. We present a case of a neonate with CDH and severe PH where variance in transductal flow patterns negatively impacted veno-arterial ECMO (VA-ECMO) circuit efficiency.

## Case

A male infant was born at 37 weeks and 6 days gestation and weighted 2,893 grams to a 25-year-old G2, P1 lady. The pregnancy was complicated by maternal gestational hypertension, Factor V Leiden heterozygous status, and Ehlers-Danlos syndrome. Antenatal fetal ultrasound imaging showed evidence of intrauterine growth restriction (IUGR) and left-sided CDH with a small left ventricle presumed secondary to intrathoracic compression. The lung-to-head ratio (LHR) by fetal ultrasound at 32-week gestational age (GA), a predictor of survival, was 0.9, which equates to an observed/expected (O/E) LHR of 22%. For fetuses with isolated left CDH and O/E LHR of 25% or lower, survival rates were below 30% [10]. The patient was born by normal vaginal delivery. Apgar scores were 3 and 8 at 1 and 5 minutes, respectively. Resuscitation included immediate intubation and assisted respiratory support. The patient was initially started on conventional synchronized intermittent mandatory ventilation (SIMV): initial settings were peak inspiratory pressure (PIP) of 31 $cmH_2O$, positive end-expiratory pressure (PEEP) of 5 $cmH_2O$, ventilatory rate (R) of 40, pressure support (PS) of 14 $cmH_2O$, inspiratory time (iT) of 0.5 seconds and fractional inspired oxygen ($FiO_2$) of 1.0. The patient was converted to high-frequency oscillatory ventilation (HFOV) (mean airway pressure [MAP] of 15 $cmH_2O$, frequency [F] of 10, power [P] of 3.5, and iT of 33%) at 1 hour due to persistent respiratory acidosis (pH 7.11, $PCO_2$ 85, $PaO_2$ 42, BE -3). Subsequently, arterial $CO_2$ improved (target 50-60 mmHg), and $FiO_2$ dropped to 0.3. The first targeted neonatal echocardiography (TnECHO) at 1 hour showed supra-systemic PH with severe right ventricular systolic dysfunction but evidence of left-to-right atrial level shunting suggestive of a left heart phenotype. Therefore, the patient was started on intravenous epinephrine 0.05 mcg/kg/min and PGE1 0.01 mcg/kg/min. Serial hemodynamic evaluations were subsequently performed (**Tab. 1**).

The patient developed a progressive increase in $FiO_2$ requirement in the next 24 hours despite continued optimization of respiratory support. Repeat TnECHO showed improved heart function but evidence of ongoing supra-systemic pulmonary

**Table 1.** Serial targeted neonatal echocardiography (TnECHO) evaluations.

| Postnatal age (d) | Pulmonary pressures | PDA size and direction | PFO/ASD | LV | RV |
|---|---|---|---|---|---|
| **0** | Supra-systemic PH (estimated RVSp of at least 52 mmHg + RAp). | Large PDA [6.5 mm] with bidirectional (90% right-to-left) shunt. | Small PFO/ASD with bidirectional shunt. | Normal sized LV and systolic function [EF 76% by Simpsons biplane] with LVO of 40 mL/min/kg. | Dilated RV [RV:LV area 1.0] with moderately reduced RV systolic function [TAPSE 4.0, RV FAC 0.27, RV S' 3.97]. RVO of 62 mL/min/kg. |
| **1** | Supra-systemic PH (incomplete TR jet). | Large PDA [5 mm] with bidirectional (mostly right-to-left) shunt. | Small PFO/ASD with left-to-right shunt. | Normal LV size and systolic function [EF 72% by Simpsons biplane] with LVO 125 mL/min/kg. | Dilated RV [RV:LV area 1.1] with normal RV systolic function [TAPSE 9.5, FAC 0.53, RV S' 6.6]. RVO 168 mL/min/kg. |
| **2** | Supra-systemic PH (estimated RVSp of at least 66 mmHg + RAp). | Large PDA [6 mm] with bidirectional (mostly right-to-left) shunt. | Small PFO/ASD with left-to-right shunt. | Normal LV size and systolic function [EF 69% by Simpsons biplane] with LVO 77 mL/min/kg. | Normal RV size [RV:LV area 0.36] and systolic function [TAPSE 10.7, FAC 0.53, RV S' 6.1]. RVO 203 mL/min/kg. Elevated PVRi [RVET:PAAT 5.7]. |
| **3** | Systemic level PH (incomplete TR jet). | Large PDA [6.4 mm] with bidirectional shunt. | Tiny PFO/ASD with left-to-right shunt. | Normal LV size and systolic function [EF 85% by Simpsons biplane] with LVO 94 mL/min/kg. | Normal RV size [RV:LV area 0.43] and systolic function [TAPSE 9.3, FAC 0.49, RV S' 6.7]. RVO 128 mL/min/kg. Elevated PVRi [RVET:PAAT 4.9]. |
| **3 (iNO trial 20 ppm)** | Systemic level PH (incomplete TR jet). | Large PDA [7.4 mm] with bidirectional shunt. | Tiny PFO/ASD with left-to-right shunt. | Normal LV size and systolic function [EF 63% by Simpsons biplane] with LVO 100 mL/min/kg. | Normal RV size and systolic function [TAPSE 8.6, FAC 0.32, RV S' 6.5]. RVO 122 mL/min/kg. Elevated PVRi [RVET:PAAT 5.4]. |
| **5** | Systemic level PH (incomplete TR jet). | Large PDA [8.0 mm] with predominately left-to-right shunt. | Small PFO/ASD with left-to-right shunt. | Normal LV size and systolic function [EF 73% by Simpsons biplane] with LVO 128 mL/min/kg. | Normal RV size [RV:LV area 0.29] and systolic function [TAPSE 10.3, FAC 0.35, RV S' 6.1]. RVO 108 mL/min/kg. Elevated PVRi [RVET:PAAT 5.1]. |
| **6** | Systemic level PH (incomplete TR jet). | Large PDA [8.0 mm] with bidirectional shunt. | Small PFO/ASD with bidirectional shunt. | Normal LV size and systolic function [EF 70% by Simpsons biplane] with LVO 104 mL/min/kg. | Normal RV size [RV:LV area 0.42] and systolic function [TAPSE 8.2, FAC 0.34, RV S' 4]. RVO 127 mL/min/kg. |

ASD: atrial septal defect; EF: ejection fraction; FAC: fractional area change; iNO: inhaled nitric oxide; LV: left ventricle; LVO: left ventricular output; PAAT: pulmonary artery acceleration time; PDA: patent ductus arteriosus; PFO: patent foramen ovale; PH: pulmonary hypertension; ppm: part per million; PVRi: pulmonary vascular resistance index; RAp: right atrium pressure; RV: right ventricle; RVET: right ventricular ejection time; RVO: right ventricular output; RVSp: right ventricular systolic pressure; S': pulsed wave tissue Doppler S wave (systolic excursion velocity); TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation.

artery pressure and a bidirectional atrial level shunt. A trial of inhaled nitric oxide (iNO) was therefore initiated, starting with a dose of 5 parts per million (ppm), which was increased to 20 ppm. There was neither clinical nor echocardiography response and the patient continued to require high $FiO_2$, and the atrial level shunt continued to be bidirectional; therefore, iNO was weaned off. Intravenous milrinone 0.33 mcg/kg/min was started on postnatal day 2 to provide enhanced vasodilator support, and vasopressin 0.3 mu/kg/min was added to support systemic blood pressure. The patient continued to have refractory hypoxemic respiratory failure ($FiO_2$ 1.0 and oxygenation index [OI] of 42.5) despite augmentation of milrinone to 1 mcg/kg/min and systemic hypotension despite the escalation of vasopressin to 2 mu/kg/min. The infant continued to have systemic-level pulmonary pressures with normal biventricular function. The decision was made to cannulate onto VA-ECMO on postnatal day 6.

Both arterial and venous cannulae were noted to be well positioned on post-initiation echocardiography. ECMO flow was initiated and increased gradually to 100 mL/kg/min. The HFOV was placed in rest settings (MAP of 12 cm $H_2O$, F of 12, P of 1.2), and the cardiovascular treatment was adjusted accordingly (intravenous epinephrine of 0.04 mcg/kg/min, PGE1 of 0.005 mcg/kg/min, milrinone of 0.46 mcg/kg/min, and iNO of 5 ppm). Ten hours after initiation of ECMO, there were multiple episodes of circuit chugging and intermittent loss of flow, which was managed with normal saline fluid boluses; specifically, over 36 hours, the patient received a total of 250 mL/kg of fluid boluses, given in increments of 5-10 mL/kg. A difference of 20 mmHg between pre-ductal (higher) and post-ductal systolic BP was suggestive of increased left-to-right flow across the PDA. In addition, urine output decreased from 11 to 5 mL/kg/hr. Arterial blood gas (post-ductal umbilical arterial line) analysis showed normal pH and $pCO_2$ but $PaO_2$ of 150 mmHg. The ECMO settings were ~120 mL/kg/min of flow with a sweep of 0.7 and $FiO_2$ 0.45, while the mixed venous oxygen saturation ($SVO_2$) was 80%. The patient's blood workup was otherwise unremarkable, with plasma Na 145, Hg 17.3 g/dL, and platelet count of 146 K/μL. Repeat TnECHO evaluation showed that both venous and arterial cannulae were in good positions and without evidence of clot formation. There was, however, evidence of a large (5 mm) hemodynamically significant PDA with an unrestrictive pulsatile left-to-right shunt, holodiastolic flow reversal in the post-ductal descending aorta and an underfilled right atrium (**Fig. 1**).

Based on the TnECHO findings, iNO was weaned to 2 ppm, milrinone was weaned to 0.2 mcg/kg/min, but the PGE1 was maintained at the same dose. In addition, the target patient's post ductal

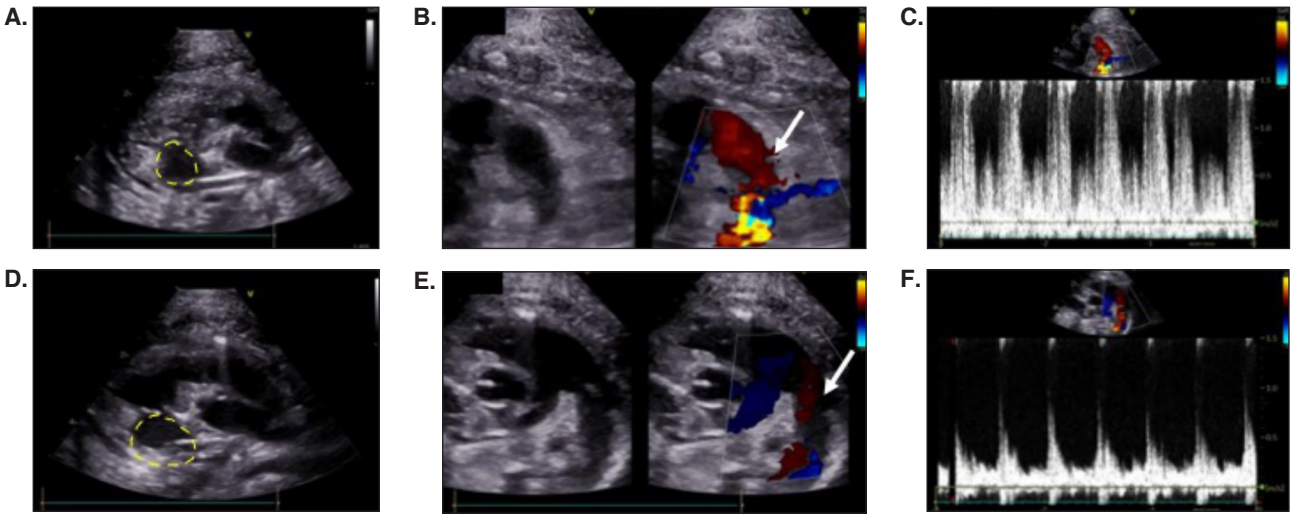


**Figure 1.** Echocardiography assessment of patent ductus arteriosus (PDA) shunt magnitude on extracorporeal membrane oxygenation (ECMO) pre and post shunt modulation strategies.

Panels **A-C** demonstrate a pulsatile high velocity left-to-right shunt across a large PDA. Panels **D-F** demonstrate a reduction in peak velocity across the PDA after implementation of shunt modulation strategies. Panel **A**: Subcostal view of the venous cannula in the right atrium (RA) depicted as the area highlighted as yellow. Panel **D** shows an increase in RA size. Panel **B**: Parasternal short axis view shows a large PDA with left-to-right flow (red color). Panel **E** shows a large PDA with less left-to-right flow (less red color). Panel **C**: Pulse wave Doppler of the large PDA show high velocity (~1.5 m/s) pulsatile left-to-right shunt. Panel **F**: Pulse wave Doppler of the large PDA show low velocity (0.5 m/s) pulsatile left-to-right shunt.

umbilical blood gas parameter targets were adjusted to $PaO_2$ 50-100 mmHg and $PCO_2$ 50-60 mmHg to increase pulmonary vascular resistance (PVR) and limit the magnitude of the transductal shunt. Repeat TnECHO evaluation 8 hours later showed that the right atrium was subjectively larger in size and, although the PDA remained large and left-to-right, the peak velocity decreased from approximately 1.5 m/s to 0.5 m/s consistent with decreased transductal pressure gradient (**Fig. 1**). iNO decreased further to 1 ppm, but milrinone and PGE1 were maintained at the same doses due to equilibration of left and right ventricular outputs as the magnitude of the left-to-right shunt decreased. No further chugging was observed, and the remainder of the ECMO run was uneventful. The patient was decannulated successfully on postnatal day 20.

## Discussion

Refractory hypoxemic respiratory failure in the setting of CDH is a common reason for ECMO in neonates [11]. As intravenous prostaglandin is often used in the settings of CDH to optimize right ventricular systolic function, many patients will have a PDA at the time of cannulation. After cannulation, patients often experience abrupt enhancement in oxygenation and ventilation, resulting in pulmonary vasodilation. In addition, as many patients may remain on systemic vasoconstrictors (such as dopamine, epinephrine, and vasopressin) and medications with pulmonary vasodilator properties (such as iNO, PGE1, and milrinone), the magnitude of left-to-right transductal flow may increase. This may not be obvious clinically or considered physiologically, as longitudinal echocardiography is not always performed. Therefore, as blood is withdrawn from the right atrium via the venous cannula, pulmonary arterial pressure will drop. In the presence of a wide-open PDA, increased systemic-pulmonary shunting may lead to compromised post-ductal blood flow thereby creating "relative hypovolemia" of the right heart, which can lead to the potential of circuit chugging.

ECMO flow-related problems are well described both in the veno-venous (VV-) and VA-ECMO setting [7, 8, 9, 12, 13]. Suboptimal venous return can result from hypovolemia, vasodilation, or inflow obstruction. Low flow states may relate to inadequate cannula position, cannula-related thrombus, or hypovolemia [14-16]. In cases where a cannula is placed in the superior vena cava or right atrium, increases in intrathoracic or pericardial pressure may compromise venous return. Excessively negative drainage pressure occurs when the pump speed is set too high relative to inflow resistance and blood volume. The timing of flow insufficiency may vary throughout the ECMO course, from early-onset due to vasodilation or cannulation issues to later-onset during ECMO support due to agitation or volume removal [17].

Previous studies have investigated the relevance of left-to-right PDA shunt in patients during ECMO. Tanke et al. demonstrated that patients with a persistent large left-to-right shunt have a longer ECMO run, which they speculate relates to prolonged exposure to excessive pulmonary blood flow [8]. Further, Lotze et al. demonstrated impaired lung compliance and chest radiograph "white-out" due to pulmonary overcirculation in the context of a left-to-right shunt [18]. Low systemic venous return is possible in patients with a large PDA and high-volume left-to-right shunt; therefore, appreciation of the determinants of transductal flow is important (**Fig. 2**).

According to the Hagen-Poiseuille principle, flow is determined by the vessel length and radius, pressure gradient, and blood viscosity [19]. Consequently, interventions that increase PDA diameter (e.g., prostaglandin), decrease PVR (such as high $PaO_2$, low $PCO_2$, iNO), increase systemic vascular resistance (e.g., dopamine, norepinephrine, vasopressin) or decrease blood viscosity (e.g., low hemoglobin or platelet count) may increase the magnitude of the systemic-to-pulmonary (left-to-right) shunt leading to decreased right atrial volume loading. Tissue oxygenation in patients undergoing ECMO is influenced by various factors, including $SvO_2$, hemoglobin concentration, native lung function, ventilator $FiO_2$, PEEP, and ECMO flow and oxygenation. In VA-ECMO, $SvO_2$ is a reliable indicator of sufficient oxygen delivery to end organs, with a target range of 65-80%. While it is crucial to prevent both hypoxemia and hyperoxemia, elevated $PaO_2$ levels in the presence of a large PDA may result in excessive reduction in PVR and increased left-to-right shunting, potentially leading to post-ductal hypoperfusion [20]. Hence, if arterial $PaO_2$ exceeds 100 mmHg, circuit flow or sweep gas $FiO_2$ adjustments should be made accordingly [21].

In this patient, the temporal relationship of a large left-to-right PDA shunt and circuit chugging may have been related to the cumulative effects of high $PaO_2$, receipt of iNO, intravenous milrinone, and PGE1, all of which are potent pulmonary vasodilators. The use of fluid boluses may have

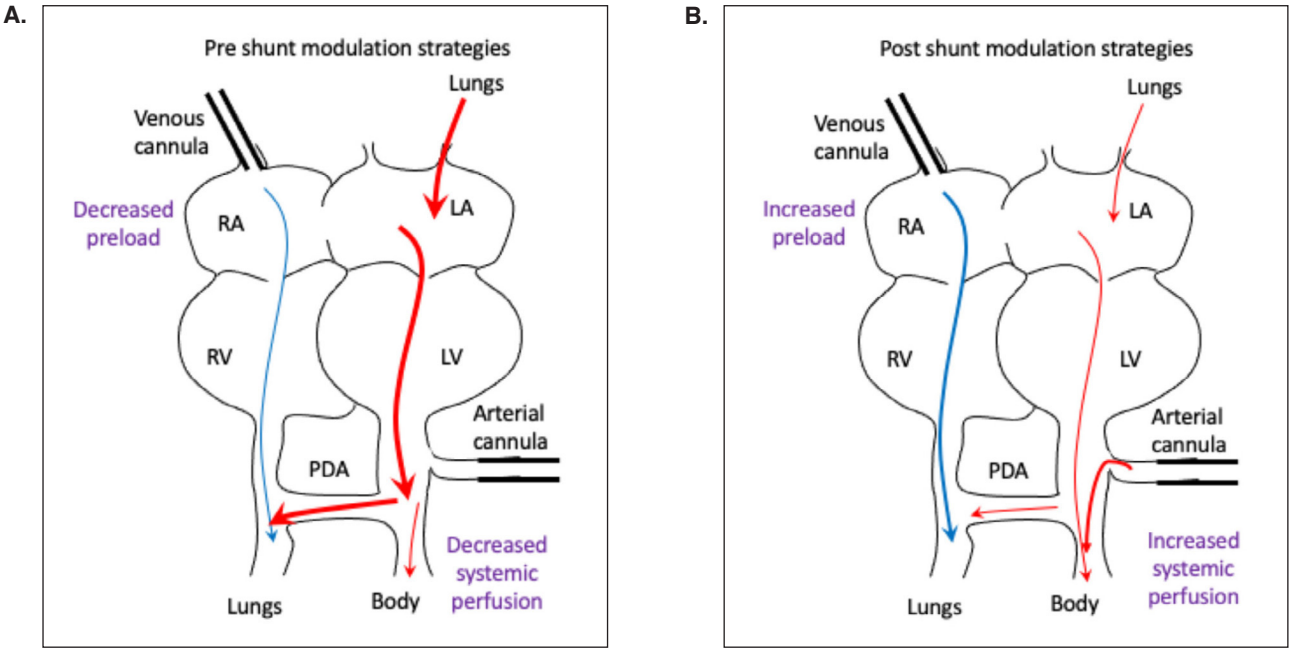


**Figure 2.** Schematic showing changes in right atrial preload and post-ductal perfusion according to flow patterns across a patent ductus arteriosus (PDA).

**A.** In the presence of a large left-to-right shunt, there is evidence of decreased post-ductal systemic perfusion which drives decreased right atrial preload. **B.** After implementation of shunt manipulation strategies, the magnitude of the left-to-right shunt decreases leading to increased systemic blood flow; hence, right atrial preload will increase leading to enhanced right atrial volume loading diminishing the risk of circuit chugging.

LA: left atrium; LV: left ventricle; PDA: patent ductus arteriosus; RA: right atrium; RV: right ventricle.

provided temporary augmentation of the right heart preload and resolution of the chugging, but the primary physiologic concern (high-volume PDA shunt) remained. Targeting lower $PaO_2$ and weaning the iNO was followed by the resolution of circuit chugging and balancing of the transductal shunt without the need to increase the ECMO flow. Intravenous PGE1 is used in neonates with severe CDH and life-threatening PH to maintain ductal patency to avoid excessive pressure/volume loading and systolic dysfunction of the right ventricle in the early stabilization period or after surgical intervention [22, 23]. We elected not to discontinue the intravenous PGE1 infusion as the dose was already extremely low, and the standard of care at our center is to maintain ductal patency until after surgical intervention.

It is the strategy in some centers to increase the ECMO flow in the presence of patent aorto-pulmonary shunt to compensate for the shunt run-off [13, 24]. While such approach may achieve adequate systemic and pulmonary flow, it may lead to fluid overload further complicating the ECMO run. Indeed, patients who demonstrated left ventricle dilation in the course of ECMO secondary to excessive left-to-right shunt were unable to wean from ECMO due to pulmonary edema prompting ductal ligation before they could be weaned from ECMO [9]. An observational study [25] demonstrated an association between fluid overload at CRRT initiation and mortality in pediatric patients receiving ECMO. Furthermore, correcting fluid overload to ≤ 10% was not associated with improved survival. These results suggest that intervening prior to the development of significant fluid overload may be more clinically effective than attempting fluid removal after significant fluid overload has developed. In addition, careful delineation of the cause of circuit chugging and the need for fluid boluses may minimize the magnitude of volume overload. There are, however, no published data characterizing the medical management or restriction of the PDA shunt to regulate the flow during ECMO.

Extracorporeal Life Support Organization guidelines on managing pediatric ECMO recommend that an echocardiography-trained physician should be part of the team caring for neonates and children on ECMO [26]. Echocardiography during ECMO can help monitor cardiac chamber size to ensure adequate emptying of the cardiac chambers [27-31]. TnECHO has been increasingly used in the management of newborns with cardiovascular compromise, including patients

supported with ECMO; specifically, TnECHO refers to a comprehensive echocardiography evaluation of myocardial function, systemic and pulmonary blood flow, intracardiac and extracardiac shunts, organ blood flow and tissue perfusion [32]. It is performed as part of a "hemodynamic consultation" that refers to a comprehensive, integrated assessment by a neonatologist with advanced echocardiography skills and a strong foundation in neonatal pathophysiology [33]. In this patient, serial TnECHOs enhanced characterization of the ambient hemodynamics, allowing refinement of the cardiovascular support before and after cannulation. In particular, serial TnECHO evaluation helped to delicately manage the flow across the PDA to optimize oxygenation and maintain the flow in the circuit at low ECMO flow settings.

## Conclusion

In summary, clinicians should consider the role of the PDA in managing patients on ECMO. Serial TnECHOs may enable better hemodynamic monitoring and management; however, there are little normative data to guide practice, which represents a knowledge gap.

## Declaration of interest

The Authors declare that there is no conflict of interest.

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